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Health and Environmental Effects Profile for Dichloroethenes

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16. ABSTRACT

The Health and Environmental Effects Profile for Dichloroethenes was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Existing data are insufficient to determine an Acceptable Daily Intake (ADI) or a carcinogenic potency factor for dichloroethenes.

The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. The RQ value for 1,1- and 1,2-dichloroethene is 1000.

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR DICHLOROETHENES

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constit- uents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched."

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA docket.

ACKNOWLEDGEMENTS

The initial draft of this report was prepared by Syracuse Research Corporation under Contract No. 68-03-3228 for U.S. EPA's Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. Dr. Christopher DeRosa was the Technical Project Monitor and Helen Ball was the Project Officer. The final documents in this series were prepared for the Office of Solid Waste, Washington, DC.

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EXECUTIVE SUMMARY

The dichloroethenes are colorless volatile liquids with characteristic odors (Gibbs and Wessling, 1983; Stevens, 1979). 1,1-Dichloroethene, more commonly known as vinylidene chloride, is predominantly used in the manufacture of copolymers (Gibbs and Wessling, 1983); the principal copolymer produced by Dow Chemical is Saran®. Current production of 1,1-dichloroethene is >200 million pounds annually (Gibbs and Wessling, 1983). Commercially produced 1,2-dichloroethene is a mixture of the trans- and cis-isomers and is usually produced as a by-product in the chlorination of other compounds (Stevens, 1979). The most important commercial use of 1,2-dichloroethene is probably as a chemical intermediate in the manufacture of other chlorinated solvents and compounds (Stevens, 1979). It can also be used as a low-temperature extraction solvent for organic materials (Stevens, 1979). Both the trans- and cis-isomers of 1,2-dichloroethene are present as impurities in commercial-grade 1,1-dichloroethene (Fishbein, 1979).

Volatilization is likely to be the dominant fate mechanism for dichloroethenes in environmental surface waters. Hydrolysis, oxidation, direct photolysis and bioaccumulation are not expected to be important processes in water. In general, the dichloroethene molecule may be stable to microbial bio-oxidative action (Tabak et al., 1981). The persistence in groundwater is expected to be significantly longer than in surface water since volatilization may not be the major pathway for disappearance in groundwater.

In the atmosphere, reaction with hydroxyl radicals is expected to be the dominant fate process; a half-life of ~2.6 days has been theoretically estimated for the dichloroethenes (U.S. EPA, 1986).

Based on log K_{ow} values, water solubilities and molecular topology, the dichloroethenes may be expected to leach significantly in many soil types. Volatilization from soil surfaces may be important.

The dichloroethenes have been detected in widespread samples of ambient water (Westrick et al., 1984) and ambient air. These compounds may be emitted to environmental waters through industrial effluents, leaching (Sabel and Clark, 1984) and microbial degradation of 1,1,1-trichloroethane to yield dichloroethene (Smith and Dragun, 1985; Parsons et al., 1984). The major atmospheric emission source of 1,1-dichloroethene has been reported to be the copolymer production of Saran® (Harkov et al., 1983); additional sources include other industrial sources (Weant and McCormick, 1984), combustion sources (Cooke et al., 1984) and volatilization from contaminated waters. Foodstuffs packaged with Saran® film wrapping have been found to be contaminated by unreacted 1,1-dichloroethene remaining in the polymer film, although the concentrations found in the foods were small (Gilbert et al., 1980).

The information concerning the aquatic toxicity of dichloroethenes is limited. Results of studies with bluegills and Daphnia magna suggest that 1,1-dichloroethene is about twice as acutely toxic as 1,2-dichloroethene (U.S. EPA, 1978). Daphnia magna was the most sensitive species tested, having a NOEC of <2.4 mg/ℓ (LeBlanc, 1980; U.S. EPA, 1978). The only chronic toxicity data available indicated that fathead minnows were unaffected by concentrations of ≤2.8 mg/ℓ in an embryo-larval test. Two algal species tested were less susceptible to the effects of 1,1-dichloroethene exposure than any of the animal species (U.S. EPA, 1978).

Gastrointestinal absorption of 1,1-dichloroethene by rats appears to be rapid and relatively complete (McKenna et al., 1978; Jones and Hathway,

1978a; Reichert et al., 1979; Anderson et al., 1979). Pulmonary absorption appears to be biphasic with a rapid first-order phase (independent rate constant) representing tissue equilibration and the second slower concentration-dependent phase associated with metabolism (Anderson et al., 1979). Distribution of absorbed 1,1-dichloroethene throughout the body occurs rapidly, with the highest levels occurring in the liver and kidneys (McKenna et al., 1978; Jones and Hathway, 1978a; Jaeger et al., 1977). Significant accumulation of the compound does not appear to occur. 1,1-Dichloroethene is metabolized in the liver with a number of possible reactive intermediates, including an epoxide (1,1-dichloroethylene oxide), being formed (U.S. EPA, 1985). These reactive intermediates may react with macromolecules and are detoxified primarily by conjugation with glutathione. Elimination of metabolites and unmetabolized 1,1-dichloroethene occurs primarily through the urine, with up to 70-80% of the absorbed oral and inhalation doses excreted within 24 hours (Jones and Hathway, 1978a; Reichert et al., 1979; McKenna et al., 1978). Exhalation of unchanged 1,1-dichloroethene and CO_2 and fecal elimination can account for up to 10-15% of the absorbed dose, but at high dosage/exposures much higher percentages are exhaled as unmetabolized 1,1-dichloroethene, suggesting that metabolism is rate-saturable. Biliary excretion accounts for a substantial proportion of administered compound, but metabolites excreted in the bile appear to be nearly completely reabsorbed and eventually excreted in the urine.

Information regarding the absorption, distribution or elimination of cis- or trans-1,2-dichloroethene could not be located in the available literature as cited in the Appendix. Limited evidence indicates that metabolism proceeds by epoxidation with rearrangement to form 1,1-dichloroacetaldehyde (Henschler, 1977; Liebman and Ortiz, 1977).

There is limited evidence for the carcinogenicity of 1,1-dichloroethene. Significantly increased incidences of kidney adenocarcinomas, a rare tumor type, occurred in male Swiss mice exposed to 25 ppm 1,1-dichloroethene 4 hours/day, 5 days/week for 52 weeks followed by lifetime observation (Maltoni et al., 1985). Carcinogenicity of 1,1-dichloroethene was not demonstrated in numerous other studies with mice (strains other than Swiss), rats or hamsters, including NTP (1982) gavage bioassays with mice and rats. Activity as a tumor initiator in mouse skin, however, has been reported (Van Duuren et al., 1979). A retrospective mortality study of a cohort of 138 1,1-dichloroethene workers did not find exposure-related carcinogenicity, but design limitations preclude definite conclusions of noncarcinogenicity. Information regarding the carcinogenicity of 1,2-dichloroethene could not be located in the available literature as cited in the Appendix.

Mutagenicity of 1,1-dichloroethene has been demonstrated in numerous assays with different strains of S. typhimurium (Bartsch et al., 1975, 1979; Oesch et al., 1983; McCarroll et al., 1983; Jones and Hathway, 1978b; Cerna and Kypenova, 1977; Baden et al., 1976, 1977, 1978; Simmon et al., 1977; Malaveille et al., 1977; Waskell, 1978). 1,1-Dichloroethene also produced reverse mutation in E. coli WP2uvrA (Jones and Hathway, 1978b), reverse mutations at the arg^+ locus in E. Coli K12 (Greim et al., 1975) and mutations in the yeast S. cerevisiae D7 (Bronzetti et al., 1981). 1,1-Dichloroethene has been reported to induce SCEs in cultured Chinese hamster ovary cells (McCarroll et al., 1983), but did not produce mutations to 8-azoquanine or oubain resistance in cultured V79 Chinese hamster cells (Drevon and Kuroki, 1979), dominant lethal mutations in rats (Short et al., 1977a) or mice (Anderson et al., 1977) exposed by inhalation, or chromosomal aberrations in bone marrow cells of mice exposed by inhalation (Cerna and

Kypenova, 1977). Limited evidence suggests that cis-1,2-dichloroethene is mutagenic when tested with *in vivo* metabolic activation systems. Mutagenicity was reported in host-mediated assays with *S. typhimurium* (Cerna and Kypenova, 1977) and *S. cerevisiae* (Bronzetti et al., 1984), but activity was not demonstrated with the trans-isomer in the same studies. cis-1,2-Dichloroethene and trans-1,2-dichloroethene were not mutagenic in reverse mutation assays with *S. typhimurium* (Cerna and Kypenova, 1977), forward and reverse mutation assays with *E. coli* (Greim et al., 1975) or assays with *S. cerevisiae* (Galli et al., 1982; Bronzetti et al., 1984) when tested with or without added metabolic activation preparations. Repeated intraperitoneal injections of cis-1,2-dichloroethene to mice produced chromosomal aberrations in the bone marrow, but similar treatment with the trans-isomer was not clastogenic (Cerna and Kypenova, 1977).

Teratogenic effects were not observed in the offspring of rats exposed to 200 ppm (200 mg/ℓ) 1,1-dichloroethene in the drinking water, or in offspring of rats or rabbits exposed by inhalation to ≤160 ppm (630 mg/m³), 7 hours/day on days 6-15 of gestation (Murray et al., 1979). Embryo/fetotoxicity was evident among the rats that inhaled 80 or 160 ppm (320 or 630 mg/m³) (delayed ossification of skull and cervical vertebrae centra, wavy ribs) and rabbits that inhaled 160 ppm (increased resorptions), but these effects did not occur without maternal toxicity. Incomplete ossification of fetal sternebrae and maternal toxicity occurred in another inhalation study with rats exposed to 15-449 ppm (59-1780 mg/m³) and mice exposed to 15-300 ppm (59-1190 mg/m³) 1,1-dichloroethene for 23 hours/day on days 6-16 of gestation (Short et al., 1977b). A 3-generation reproduction study showed that drinking water containing 50-200 ppm (50-200 mg/ℓ) 1,1-dichloroethene produced hepatotoxic effects in adult rats but no effect on reproduction or

neonatal development (Nitschke et al., 1980). Information regarding teratogenicity or other reproductive effects of 1,2-dichloroethene could not be located in the available literature as cited in the Appendix.

Chronic oral or inhalation administration of 1,1-dichloroethene to rats and mice produced toxic effects primarily in the liver. Hepatic alterations that include congestion, hypertrophy, hemorrhages, fatty degeneration, atrophy and necrosis were described in mice exposed by gavage to 10 mg/kg/day, 5 days/week for 104 weeks (NTP, 1982), rats exposed continuously by drinking water to 50-200 ppm (50-200 mg/ℓ) for 2 years (Rampy et al., 1977; Humiston et al., 1978; Quast et al., 1983), rats exposed by gavage to 50 mg/kg, 1 day/week for 120 weeks (Ponomarkov and Tomatis, 1980), rats exposed by inhalation to ~25 or 75 ppm (~100 or 300 mg/m³), 6 hours/day, 5 days/week for 18 months with 6 months observation (Rampy et al., 1977; McKenna et al., 1982; Quast et al., 1986), and rats and mice exposed by inhalation to 55 ppm (220 mg/m³), 6 hours/day, 5 days/week for 12 months (Lee et al., 1977). Kidney alterations including chronic inflammation in rats exposed by gavage to 5 mg/kg/day, 5 days/week for 104 weeks (NTP, 1982) and congestion in rats exposed by gavage to 50 mg/kg once weekly for 120 weeks (Ponomarkov and Tomatis, 1980) have also been reported. Hong et al. (1981) observed increased mortality and early terminations that were due to moribundity in rats and mice during 12-month observation periods following inhalation exposure to 55 ppm (220 mg/m³) 1,1-dichloroethene, 6 hours/day, 5 days/week for 10 months (rats) or 6 months (mice). Adenomatous hyperplasia of the respiratory epithelia was observed in hamsters exposed to 25 ppm (100 mg/m³) 1,1-dichloroethene, 4 hours/day, 4-5 days/week for 52 weeks with 105 weeks observation (Maltoni et al., 1985). Continuous inhalation exposure to 47 ppm (190 mg/m³) 1,1-dichloroethene for 90 days

produced depressed growth in rats, guinea pigs, rabbits, monkeys and dogs, increased liver alkaline phosphaste and SGPT activities in rats and guinea pigs, hepatic effects including fatty changes and necrosis in rats, monkeys and dogs, and hypertrophy of the renal tubule epithelium in rats (Prendergast et al., 1967). Nonacute toxicity data for 1,2-dichloroethene are limited to two conflicting subchronic inhalation toxicity studies. An unpublished report indicates that exposure to 500 or 1000 ppm (2000 or 4000 mg/m^3) 1,2-dichloroethene (60% cis- and 40% trans-isomer mixture) for 6 months (7 hours/day, 5 days/week) did not produce adverse effects on numerous parameters in rats, rabbits, guinea pigs or dogs (Torkelson, 1965). Freundt et al. (1977) reported fatty changes in the liver and pulmonary damage in rats exposed to 200 ppm (800 mg/m^3) trans-1,2-dichloroethene (8 hours/day, 5 days/week) for 16 weeks.

1,1-Dichloroethene was classified with regards to carcinogenic potency in IARC Group 3 and CAG Group C (U.S. EPA, 1984): possibly carcinogenic to humans. The U.S. EPA (1985) derived a q_1^* of 1.16 (mg/kg/day)$^{-1}$ from the incidence of kidney adenocarcinomas in male mice exposed by inhalation (Maltoni et al., 1985). Several q_1^*s were calculated from oral studies, the highest of which was 0.577 (mg/kg/day)$^{-1}$, based on the incidence of adrenal pheochromocytomas in male rats in an NTP (1982) gavage experiment. An F factor of 101.2 (mg/kg/day)$^{-1}$ was calculated from the inhalation data, resulting in a CERCLA ranking in Potency Group 1. A CS of 19 corresponding to an RQ of 1000 was calculated for 1,1-dichloroethene based on increased mortality and moribundity in mice exposed by inhalation for 6 months followed by a 12-month postexposure observation period (Hong et al., 1981).

1,2-Dichloroethene was classified in IARC Group 3 and CAG Group D: Not classified. No ADI was derived for either the cis- or the trans-isomers because of unexplained discrepancies in the results of inhalation experiments. A CS of 13.8, corresponding to an RQ of 1000, was calculated for 1,2-dichloroethene based on fatty infiltration of the liver and histological alterations in the lungs of rats exposed by inhalation for 16 weeks (Freundt et al., 1977).

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
BCF	Bioconcentration factor
BOD	Biological oxygen demand
CAS	Chemical Abstract Service
CS	Composite score
DNA	Deoxyribonucleic acid
EC_{50}	Concentration effective to 50% of recipients
K_{oc}	Soil sorption coefficient
K_{ow}	Octanol/water partition coefficient
LC_{50}	Concentration lethal to 50% of recipients
LD_{50}	Dose lethal to 50% of recipients
LOAEL	Lowest-observed-adverse-effect level
MED	Minimum effective dose
MTD	Maximum tolerated dose
NOAEL	No-observed-adverse-effect level
NOEC	No-observed-effect concentration
ppb	Parts per billion
ppm	Parts per million
RQ	Reportable quantity
RV_d	Dose-rating value
RV_e	Effect-rating value
SCE	Sister-chromatid exchange
SGPT	Serum glutamic pyruvic transaminase
STEL	Short-term exposed level
TLV	Threshold limit value
TWA	Time-weighted average
UV	Ultraviolet

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

The synonyms, CAS Registry numbers, molecular weights and empirical formulas and structures of the dichloroethenes are listed in Table 1-1. The CAS number for 1,2-dichloroethene (combination of both the cis- and trans-isomers) is 540-59-0.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Selected physical properties of the dichloroethenes are listed in Table 1-2. 1,1-Dichloroethene is soluble in most polar and nonpolar organic solvents (Gibbs and Wessling, 1983) and its solubility in water (0.25 wt%) is nearly independent of temperature at 15-90°C (Delassus and Schmidt, 1981; Gibbs and Wessling, 1983). 1,2-Dichloroethene is soluble in alcohol, ether and most other organic solvents (Windholz, 1983).

1,1-Dichloroethene is readily polymerized at temperatures >0°C, especially in the presence of oxygen or other catalysts (Windholz, 1983); uncontrolled polymerization may lead to an explosive reaction. 1,1-Dichloroethene undergoes autooxidation in air to yield a peroxide, even in the absence of sunlight (Hardie, 1964).

In water, 1,2-dichloroethene hydrolyzes slowly with liberation of acid (Hardie, 1964). It is unaffected by weak alkalies (Stevens, 1979). The trans-isomer of 1,2-dichloroethene is more reactive chemically than the cis-isomer in 1,2-addition reactions (Stevens, 1979).

1.3. PRODUCTION DATA

Production data for the dichloroethenes available from the U.S. EPA TSCA Production File for 1977 are listed in Table 1-3. In 1976, U.S. production of 1,1-dichloroethene was 154 million pounds with an additional 110 million

TABLE 1-1

Dichloroethene Structures, CAS Numbers, Molecular Weights and Empirical Formulas

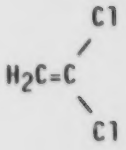
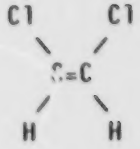
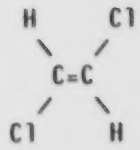
Dichloroethene (synonyms)	CAS Number	Molecular Weight	Empirical Formula	Structure
1,1-Dichloroethene (1,1-dichloroethylene) (as-dichloroethylene) (vinylidene chloride) (vinylidene chloride monomer) (1,1-DCE)	75-35-4	96.944	$C_2H_2Cl_2$	
cis-1,2-Dichloroethene (cis-1,2-dichloroethylene) (cis-acetylene dichloride) (Z-1,2-dichloroethene) (Z-1,2-dichloroethylene) (cis-sym-dichloroethylene)	156-59-2	96.944	$C_2H_2Cl_2$	
trans-1,2-Dichloroethene (trans-1,2-dichloroethylene) (trans-acetylene dichloride) (E-1,2-dichloroethene) (E-1,2-dichloroethylene) (trans-sym-dichloroethylene)	156-60-5	96.944	$C_2H_2Cl_2$	

TABLE 1-2

Physical Properties of the Dichloroethenes

Property	1,1-Dichloroethene	cis-1,2-Dichloroethene	trans-1,2-Dichloroethene
Description	colorless, mobile liquid with a characteristic sweet odor[a]	colorless, mobile liquid with an odor resembling chloroform[b]	colorless, mobile liquid with an odor resembling chloroform[b]
Melting point, °C	-122.56[a]	-81.47[b]	-49.44[b]
Boiling point, °C	31.56[a]	60.2[b]	47.7[b]
Density	1.2137 (20°C)[a]	1.2917 (15°C)[b]	1.2631 (10°C)[b]
Refractive index (20°C)	1.42468[a]	1.4490[b]	1.4462[b]
Water solubility	0.25 wt % (15-90°C)[a]	3.5 g/kg at 25°C[b] 800 ppm at 20°C[c]	6.3 g/kg at 25°C[b] 600 ppm at 20°C[c]
Vapor pressure, mm Hg	500 (20°C)[d] 591 (25°C)[c] 720 (30°C)[c]	110 (10°C)[b] 180 (20°C)[b] 200 (25°C)[d] 250 (30°C)[b]	185 (10°C)[b] 265 (20°C)[b] 320 (25°C)[d] 410 (30°C)[b]
Log K_{ow}	2.13[e]	1.86[e]	2.09[e]
Air conversion factors	1 mg/m³ = 0.25 ppm[c] 1 ppm = 3.97 mg/m³	1 mg/m³ = 0.25 ppm[c] 1 ppm = 3.97 mg/m³	1 mg/m³ = 0.25 ppm[c] 1 ppm = 3.97 mg/m³
Flash point, °C	-16 (open-cup)[a] -28 (closed-cup)	6[b]	4[b]
Ionization constant	not environmentally relevant[f]	NR	not environmentally relevant[f]

[a]Gibbs and Wessling, 1983

[b]Stevens, 1979

[c]Verschueren, 1983

[d]Engineering Sciences Data Unit, 1976

[e]Hansch and Leo, 1985

[f]Mabey et al., 1981

NR = Not reported

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TABLE 1-3

Dichloroethene Production Data for 1977*

Company/Location	Type of Production	Production Volume (pounds)
1,1-Dichloroethene		
Dow Chem./Freeport, TX	manufacturer	50-100 million
Plaquemine, LA	manufacturer	50-100 million
PPG Indust./Lake Charles, LA	manufacturer	100-500 million
Ponce, PR	manufacturer	0.1-1 million
Continental Oil Co./Westlake, LA	manufacturer	0.1-1 million
Rhone-Poulenc/New York, NY	importer	<1000
1,2-Dichloroethene (CAS No. 540-59-0)		
Dow Chem./Freeport, TX	manufacturer (captive use)	10-50 million
PPG Indust./Lake Charles, LA	manufacturer (captive use)	1-10 million
Ponce, PR	manufacturer	0.1-1 million
Continental Oil Co./Westlake, LA	manufacturer	0.1-1 million
Columbia Organics/Columbia, SC	manufacturer	<1000
cis-1,2-Dichloroethene (CAS No. 156-59-2)		
PPG Indust./Lake Charles, LA	manufacturer (captive use)	1-10 million
Ponce, PR	manufacturer	0.1-1 million

*Source: U.S. EPA, 1977

pounds produced as an unisolated intermediate in the manufacture of 1,1,1-trichloroethane (IARC, 1979). Annual U.S. production of 1,1-dichloroethene exceeds 200 million pounds (Gibbs and Wessling, 1983). The current U.S. manufacturers of 1,1-dichloroethene are Dow Chemical in Freeport, TX, and Plaquemine, LA, and PPG Industries in Lake Charles, LA (SRI, 1985).

1,1-Dichloroethene is manufactured commercially by the dehydrochlorination of 1,1,2-trichloroethane with lime or caustics (Gibbs and Wessling, 1983). Commercial grade 1,1-dichloroethene contains 200 ppm of the methyl ether of hydroquinone as a polymerization inhibitor (Gibbs and Wessling, 1983); a typical commercial grade has the following analysis (Fishbein, 1979):

1,1-dichloroethene	99.7%
cis-1,2-dichloroethene	500 ppm
trans-1,2-dichloroethene	1500 ppm
vinyl chloride	850 ppm
1,1-dichloroethane	10 ppm

1,2-Dichloroethene can be manufactured by the reduction of 1,1,2,2-tetrachloroethane or by the direct chlorination of acetylene (Hardie, 1964); however, it is often manufactured as a by-product in the chlorination of other compounds (Stevens, 1979).

1.4. USE DATA

1,1-Dichloroethene is predominantly used in the manufacture of vinylidene chloride copolymers. Approximately 150 million pounds of the monomer are converted to polymers annually in the United States (Gibbs and Wessling, 1983). The principal copolymer produced is Saran®, a tradename used by Dow Chemical; the same copolymer is also made by W.R. Grace (Daran), Union Oil (Amsco Res) and Morton Chemical (Serfene) in the United States (Gibbs and Wessling, 1983). Saran® is primarily used for food packaging films.

In addition to food and meat packaging applications, these 1,1-dichloroethene extruded resins are widely used in furniture and automobile upholstery, drapery fabric, outdoor furniture, venetian blind tape, filter cloths and chemically resistant tubing and pipe liners. 1,1-Dichloroethene lacquer resins and latexes are used in barrier coatings for a wide variety of applications (Gibbs and Wessling, 1983). 1,1-Dichloroethene is also used as a chemical intermediate in the synthesis of chloroacetyl chloride and vinylidene fluoride, but it is no longer used as an unisolated intermediate in 1,1,1-trichloroethane manufacture (Santodonato et al., 1985).

The most important commercial use of 1,2-dichloroethene is probably as a chemical intermediate in the manufacture of other chlorinated solvents and compounds (Stevens, 1979). It can be used as a low temperature extraction solvent for organic materials such as dyes, perfumes, lacquers and thermoplastics (Stevens, 1979). It has been used to extract caffeine from coffee (Hardie, 1964); however, it is not currently being used commercially for this purpose. Significant amounts of 1,2-dichloroethene have been used in Great Britain in the manufacture of rubber solutions (Hardie, 1964); it has also been used as a coolant in refrigeration plants (Hardie, 1964).

1.5. SUMMARY

The dichloroethenes are colorless volatile liquids with characteristic odors (Gibbs and Wessling, 1983; Stevens, 1979). 1,1-Dichloroethene, more commonly known as vinylidene chloride, is predominantly used in the manufacture of copolymers (Gibbs and Wessling, 1983); the principal copolymer produced by Dow Chemical is Saran®. Current production of 1,1-dichloroethene is >200 million pounds annually (Gibbs and Wessling, 1983). Commercially produced 1,2-dichloroethene is a mixture of the trans- and cis-isomers and is usually produced as a by-product in the chlorination of other

compounds (Stevens, 1979). The most important commercial use of 1,2-dichloroethene is probably as a chemical intermediate in the manufacture of other chlorinated solvents and compounds (Stevens, 1979). It can also be used as a low-temperature extraction solvent for organic materials (Stevens, 1979). Both the trans- and cis-isomers of 1,2-dichloroethene are present as impurities in commercial grade 1,1-dichloroethene (Fishbein, 1979).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. WATER

2.1.1. Hydrolysis. Pertinent data specifically regarding the rate of hydrolysis of the dichloroethenes in water could not be located in the available literature as cited in the Appendix. A study of two closely related analogues, trichloroethene and tetrachloroethene, experimentally determined the combined hydrolytic-oxidative half-lives of these compounds in a closed-aqueous system to be 8.8 and 10.7 months, respectively (Dilling et al., 1975). Mabey et al. (1981) and Jaber et al. (1984) predicted that hydrolysis is not an important environmental fate mechanism for the dichloroethenes.

2.1.2. Oxidation. Pertinent data regarding the rate of oxidation of the dichloroethenes in water could not be located in the available literature as cited in the Appendix. Trichloroethene and tetrachloroethene, however, have been shown to undergo some photooxidation in sunlit aerated water in laboratory studies (Dilling et al., 1975); however, the oxidation rates were not competitive with volatilization. Mabey et al. (1981) and Jaber et al. (1984) predicted that oxidation is not an important environmental fate mechanism for the dichloroethenes in relation to other mechanisms.

2.1.3. Photolysis. The UV absorption spectrum of 1,1-dichloroethene has a maximum at ~190 nm and decreases toward 240 nm, with only minute absorption up to 300 nm (Ausubel and Wijnen, 1976); similar absorption was also determined for cis-1,2-dichloroethene (Ausubel and Wijnen, 1975). These data indicate that direct photolysis of the dichloroethenes is not expected to occur in the environment. Mabey et al. (1981) also predicted that direct photolysis of these compounds is not environmentally relevant. Zepp and

Schlotzhauer (1983) have shown that algae may photosensitize to a small degree; however, the photodegradation of cis-1,2-dichloroethene adsorbs to the algae in aqueous solution.

2.1.4. **Microbial Degradation.** Tabak et al. (1981) examined the biodegradability of 114 organic priority pollutants to determine the extent of microbial degradation and the acclimation periods. In a static-culture flask-screening procedure using BOD dilution water containing 5 mg/ℓ yeast extract, 5 and 10 ppm concentrations of the test compound, a 7-day static incubation at 25°C followed by three weekly subcultures, and a settled domestic wastewater as microbial inoculum, 1,1-Dichloroethene was found to biodegrade significantly, with gradual adaptation. The cis- and trans-isomers of 1,2-dichloroethene underwent slow to moderate biodegradation with a significant rate of volatilization. In general, the dichloroethene molecule may be stable to microbial bio-oxidative action (Tabak et al., 1981).

The dichloroethenes can reportedly be degraded by sewage and activated sludges (Kobayashi and Rittman, 1982; Patterson and Kodukala, 1981).

2.1.5. **Volatilization.** Dilling (1977) and Dilling et al. (1975) experimentally determined the volatilization half-lives of the dichloroethenes from an open beaker containing 1 ppm aqueous concentrations of each compound at a solution depth of 6.5 cm under continuous stirring (200 rpm) as follows: 1,1-dichloroethene, 22-27 minutes; cis-1,2-dichloroethene, 18-19.4 minutes; trans-1,2-dichloroethene, 24.0 minutes.

Hine and Mookerjee (1975) reported the equilibrium air-to-water ratios of 1,2-dichloroethene in dilute aqueous solution at 25°C. From these data, the Henry's Law constants for cis-1,2-dichloroethene and trans-1,2-dichloroethene are determined to be ~3.3 and 6.6×10^{-3} atm•m³/mol, respectively.

A similar value of Henry's Law constant is expected for 1,1-dichloroethene. These values of the Henry's Law constant indicate that volatilization from environmental waters is expected to be rapid (Lyman et al., 1982).

The available data indicate that volatilization is likely to be the dominant fate mechanism in environmental surface waters. Although volatilization may be the most rapid route for removal from surface waters, it is unlikely to be a major pathway for disappearance from groundwater that is not directly exposed to air (Smith and Dragun, 1985). Therefore, the persistence of the dichloroethenes in groundwater is likely to be significantly longer than in surface water.

2.1.6. **Adsorption.** Pertinent data regarding the adsorption of the dichloroethenes by particulate organic matter and sediments in natural waters could not be located in the available literature as cited in the Appendix. The log K_{ow} values ranging from 1.86-2.13 (see Table 1-2) suggest that adsorption may not be important in relation to volatilization.

2.1.7. **Bioaccumulation.** Experimentally determined BCFs were not found for the dichloroethenes. BCFs can be estimated from log K_{ow}s using the following recommended equation (Lyman et al., 1982): Log BCF = 0.76 Log K_{ow} - 0.23. From the Log K_{ow} values in Table 1-2, the BCF values calculated for 1,1-dichloroethene, cis-1,2-dichloroethene and trans-1,2-dichloroethene are 24, 15 and 23, respectively. These BCF values indicate that the dichloroethenes are not likely to bioaccumulate significantly in aquatic organisms; the same conclusion has been suggested by Callahan et al. (1979). Gossett et al. (1983) analyzed various aquatic organisms near a wastewater discharge effluent (containing 5.2 ppb 1,2-dichloroethene) and found no significant accumulation of 1,2-dichloroethene in the organisms.

2.2. AIR

2.2.1. Photolysis. The UV absorption spectra of the dichloroethenes show no significant absorption at >300 nm (see Section 2.1.3.). Therefore, direct photolysis will not occur in the troposphere.

2.2.2. Reaction with Hydroxyl Radical. An experimentally determined rate constant was not found. Based on the chemical structure, the rate constant for the reaction between OH radicals and the dichloroethenes in the atmosphere at 25°C has been theoretically calculated to be 3.9×10^{-12} cm³/molecule-sec. (U.S. EPA, 1986). Assuming an average atmospheric OH radical concentration of 8×10^{5} molecules/cm³, a half-life of 2.6 days is calculated for this reaction. In a simulated atmospheric photodecomposition study, Dilling et al. (1976) found 1,1-dichloroethene to be somewhat more reactive than cis- or trans-1,2-dichloroethene; therefore, 1,1-dichloroethene will react more rapidly in the atmosphere than 1,2-dichloroethene, but the difference in removal rates is not likely to be significant.

The products formed from 1,1-dichloroethene in this reaction include chloroacetyl chloride, phosgene, formic acid, HCl, CO_2 and formaldehyde (Gay et al., 1976). The reaction products formed from 1,2-dichloroethene include formic acid, CO and HCl (Gay et al., 1976).

2.2.3. Reaction with Ozone. The atmospheric reaction of ozone with cis-1,2-dichloroethene yields CHClO as the major product and trans-1,2-dichloroethene as the minor product; however, the rate constant for the reaction was experimentally determined to be $<5 \times 10^{-21}$ cm³/molecule-sec, which is too small a value to be important (Niki et al., 1983).

trans-1,2-Dichloroethene reacts with ozone much faster than the cis-isomer, with a rate constant of $1.2\text{-}1.8 \times 10^{-19}$ cm³/molecule-sec (Niki

et al., 1983; Zhang et al., 1983). Peroxyformic acid was found to be the major reaction product (Niki et al., 1983; Zhang et al., 1983). Using a rate constant of 1.5×10^{-19} cm³/molecule-sec, a half-life of ~53 days can be calculated for an average atmosphere containing 10^{12} ozone molecules/cm³.

The rate constant for the reaction between ozone and 1,1-dichloroethene has been reported to be 3.7×10^{-21} cm³/molecule-sec (Tuazon et al., 1984), which is too small to be of atmospheric importance.

2.2.4. **Reaction with Atomic Oxygen.** Sanhueza and Heicklen (1975a,b) determined the following rate constants for the reaction of dichloroethenes with O(³P) at 25°C:

1,1-dichloroethene	1.0×10^{-12} cm³/molecule-sec
cis-1,2-dichloroethene	0.5×10^{-12} cm³/molecule-sec
trans-1,2-dichloroethene	1.1×10^{-12} cm³/molecule-sec

At an average O(³P) concentration of 5×10^{4} molecules/cm³, a half-life of 160 days can be calculated using a rate constant of 1×10^{-12} cm³/molecule-sec.

2.2.5. **Physical Removal Processes.** 1,2-Dichloroethene has been detected in Los Angeles rainwater at a concentration of 230 ppb (Kawamura and Kaplan, 1983), suggesting that the dichloroethenes may be removed from the atmosphere through rainfall. The significance of this process, however, is unclear; dichloroethenes removed by rainfall are susceptible to volatilization into the atmosphere.

2.3. SOIL

2.3.1. **Microbial Degradation.** Although soil bacteria have been reported to degrade 1,1-dichloroethene under anaerobic conditions (Kobayashi and Rittman, 1982), sufficient data are not available to predict the significance of the microbial degradation of the dichloroethenes in soil.

2.3.2. **Photolysis.** Since the dichloroethenes do not absorb sunlight (see Section 2.1.3.), direct photolysis on soil surfaces will not occur; however, some photosensitized photolysis that is due to adsorption to natural surfaces is possible, as demonstrated by the photodecomposition of 1,1-dichloroethene adsorbed to silica gel (Parlar, 1984).

2.3.3. **Adsorption.** Pertinent data regarding adsorption or leaching of dichloroethenes in soil could not be located in the available literature as cited in the Appendix. The Log K_{ow} values and water solubilities of the dichloroethenes (see Table 1-2) suggest that these compounds will have some mobility in soil and may be expected to leach significantly in many soil types. Estimation of K_{oc} values of the dichloroethenes by the molecular topology and quantitative structure-activity relationship analysis method of Sabljic (1984) yields a K_{oc} value of 32, which predicts high soil mobility.

2.3.4. **Volatilization.** The relatively high vapor pressures of the dichloroethenes (see Table 1-2) indicate rapid evaporation from dry surfaces. The ability of the dichloroethenes to volatilize rapidly from water (see Section 2.1.5.) suggests significant volatilization from moist soil surfaces. Therefore, volatilization may be a major transport process for the dichloroethenes in soil.

2.4. SUMMARY

Volatilization is likely to be the dominant fate mechanism for dichloroethenes in environmental surface waters. Hydrolysis, oxidation, direct photolysis and bioaccumulation are not expected to be important processes in water. In general, the dichloroethene molecule may be stable to microbial bio-oxidative action (Tabak et al., 1981). The persistence in groundwater is expected to be significantly longer than in surface water since volatilization may not be the major pathway for disappearance in groundwater.

In the atmosphere, reaction with hydroxyl radicals is expected to be the dominant fate process; a half-life of ~2.6 days has been theoretically estimated for the dichloroethenes (U.S. EPA, 1986).

Based on log K_{ow} values, water solubilities and molecular topology, the dichloroethenes may be expected to leach significantly in many soil types. Volatilization from soil surfaces may be important.

3. EXPOSURE

3.1. WATER

Dichloroethenes have been detected in ambient waters throughout the United States; monitoring data for these compounds in water are listed in Tables 3-1 and 3-2.

Westrick et al. (1984) reported the results of the U.S. EPA analysis of 945 U.S. finished water supplies using groundwater sources for the presence of volatile organic compounds. Approximately half of the finished waters served populations of <10,000 persons while the other half served populations >10,000 persons. 1,2-Dichloroethene (cis- and trans-isomer) was one of the five most frequently found compounds; it was positively detected in 5.7% of all finished waters with a median concentration (of positives) of ~1 ppb. 1,1-Dichloroethene was positively detected in 2.5% of all finished waters with a median concentration (of positives) of ~0.5 ppb.

Cole et al. (1984) reported the preliminary findings of the U.S. EPA Nationwide Urban Runoff Program to determine the presence of priority pollutants in urban stormwater runoff. Of 15 reporting cities, 1,1-dichloroethene was detected in 1 urban runoff sample (Eugene, OR) at a concentration of 1.5-4 ppb. 1,2-Dichloroethene (trans-) was found in two runoff samples (Little Rock, AK and Eugene, OR) at levels of 1-3 ppb.

Staples et al. (1985) examined the U.S. EPA STORET Data Base to assess priority pollutant concentrations in the United States. 1,1-Dichloroethene has been detected in 3.3% of industrial effluent reporting stations and in 6.0% of ambient water reporting stations. 1,2-Dichloroethene has been detected in 7.0% of industrial effluent reporting stations and in 6.0% of ambient water reporting stations.

TABLE 3-1

Water Monitoring for 1,1-Dichloroethene

Type of Water Monitored	Location	Concentration (ppb)	Comments	Reference
Cooling water	Tennessee	NR	fossil-fueled power plant	Seaman et al., 1983
River	Rhine R., Germany	<1.0	NC	Malle, 1984
Drinking	Cincinnati, OH Miami, FL Ottumwa, IO Philadelphia, PA Seattle, WA	not quantified 0.1 not detected <0.1 not detected	from National Organics Reconnaissance Survey	Coleman et al., 1976
Wastewater	Los Angeles, CA Orange, CA San Diego, CA	20 1600 <10	effluents from municipal plants	Young, 1978
Ground	Minnesota	0.5-110	contaminated by leachate from municipal solid waste landfill	Sabel and Clark, 1984
Ground and surface	New Jersey	0-17,288	ground: detected in 168/378 samples surface: detected in 197/305 samples	Page, 1981
Wastewater	Oak Ridge, TN	<10-30	effluent from gaseous diffusion plant	McMahon, 1983
Ground	Southington, CT	3800 (maximum)	contaminated by solvents recovery plant	Hall, 1984
Sediment-soil	Love Canal, NY	NR		Hauser and Bromberg, 1982
Ground	Netherlands	>0.01	3.5% of 232 stations sampled	Zoeteman et al., 1981
Wastewater	NR	<10	effluent from a petroleum refinery	Snider and Manning, 1982
Ground	Dade County, FL	2	contaminated by chemical wastes	Myers, 1983
River	Ohio River system	<10 (generally)	NC	Ohio River Valley Sanit. Comm., 1982
Ground	Nassau County, LI	0.16-1.1	NC	Connor, 1984
Surface	Lake Ontario and Niagara R.	0-3.5	not detected in 84/95 samples	Kaiser et al., 1983

TABLE 3-1 (cont.)

Type of Water Monitored	Location	Concentration (ppb)	Comments	Reference
Wastewaters, drinking well, river	various United States locations	NR	wastewaters from chemical, latex, sewage plants	Shackelford and Keith, 1976
Ground and surface	various United States locations	<1.0	2 positive detections in 103 surface samples; 1 positive detection in 13 ground samples	Coniglio et al., 1980
Ground	Sacramento, CA	NR	data submitted by Aerojet-General Corp.	U.S. EPA, 1980a

NR = Not reported; NC = no comment

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TABLE 3-2

Water Monitoring for 1,2-Dichloroethene

Type of Water Monitored	Location	Concentration (ppb)	Comments	Reference
River	Delaware and Raritan Canal, NY	24-46	NC	Granstrom et al., 1984
Wastewater	Los Angeles, CA	5.2	effluent from county treatment plant	Gossett et al., 1983
Drinking	Egypt	0.5	trans-isomer	Trussell et al., 1980
Cooling water	Tennessee	NR	fossil-fueled power plant	Seaman et al., 1983
River	England	NR	NC	Fielding et al., 1981
Ground	Lakewood, WA	485 (maximum)	trans-isomer; source of contamination identified as a commercial facility	Boating et al., 1984
Drinking	Cincinnati, OH Miami, FL Ottumwa, IO Philadelphia, PA Seattle, WA	<0.1 (cis-) ND (trans-) 14 (cis-) 1(trans-) ND 0.1 (cis-) ND (trans-) ND	from National Organics Reconnquissance Survey	Coleman et al., 1976
Wastewater	Chicago, IL	<50 (trans-)	effluent from sewage treatment plant	Lue-Hing et al., 1981
Ground	Florida	NR	groundwater beneath a leaking trichloroethene storage tank	Parsons et al., 1984
Wastewater	Los Angeles, CA Orange, CA San Diego, CA	8 <10 <10	trans-isomer; effluents from municipal plants	Young, 1978
Ground and leachate	Minnesota, Wisconsin	0.6-2200 (trans-)	leachate from municipal solid waste landfill	Sabel and Clark, 1984
Ground and surface	New Jersey	0-1308 (trans-)	ground: detected in 191/378 samples surface: detected in 172/273 samples	Page, 1981
Ground	Southington, CT	50,000 (maximum) (trans-)	contaminated by solvents recovery plant	Hall, 1984
Sediment-soil	Love Canal, NY	NR	NC	Hauser and Bromberg, 1982

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TABLE 3-2 (cont.)

Type of Water Monitored	Location	Concentration (ppb)	Comments	Reference
Runoff	Louisville, KY	75 (maximum) (trans-)	runoff from hazardous waste site	Stonebreaker and Smith, 1980
Wastewater	NR	20 (maximum) (trans-)	biological treatment effluent from petroleum refinery	Snider and Manning, 1982
Drinking	Glen Cove, NY	NA	cis-isomer	Ruggiero and Ausubel, 1980
Ground	Dade County, FL	13.3-839 (cis-)	contaminated by chemical wastes	Myers, 1983
Drinking	Philadelphia, PA	NR	NC	Suffet et al., 1976
Ground	NR	138	isomer not identified as to 1,1- or 1,2-dichloroethene; sample from vicinity of abandoned waste dumping site	Lao et al., 1982
Ground	Princeton, NJ	58	isomer not identified as to 1,1- or 1,2-dichloroethene; sample from family well	Burmaster, 1982
Drinking	Jefferson, LA	0.0007	NC	Pellizzari et al., 1979
Marine	Puget Sound, WA	2.4 (maximum)	NC	Riley et al., 1980
Wastewater, drinking, river	various United States locations	NR	wastewaters from chemical plants, sewage treatment plants, textile plants	Shackelford and Keith, 1976
Ground and surface	various United States locations	0-40	both cis- and trans-isomers detected	Coniglio et al., 1980
Ground	Sacramento, CA	NR (trans-)	data submitted by Aerojet-General Corp.	U.S. EPA, 1980a
Ground	Charlotte, NC	2295 (trans-)	data submitted by SCM Corp.	U.S. EPA, 1980b
Ground	Ft. Edward, NY	4000 (trans-)	data submitted by General-Electric Corp.	U.S. EPA, 1982

NR = Not reported; NC = no comment; NA = not available; ND = not detected

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There appear to be several sources by which ambient waters are contaminated by the dichloroethenes. Industrial effluents containing the compounds can be a direct route of exposure. trans-1,2-Dichloroethene leaches from hazardous waste (Jackson et al., 1984), and the dichloroethenes have been detected in leachate from municipal solid waste landfills (Sabel and Clark, 1984) indicating leaching as a source of groundwater contamination. Contamination of groundwater by 1,1,1-trichloroethane can result in the formation of the dichloroethenes; this is due to the microbial degradation of the trichloroethane (Smith and Dragun, 1985; Parsons et al., 1984). In addition, atmospheric "wash-out" of the dichloroethenes by rainfall may contribute to the natural water exposure.

3.2. FOOD

1,1-Dichloroethene copolymers (commonly known as Saran®) are used widely in the packaging of foods as film-coatings (Gibbs and Wessling, 1983; Gilbert et al., 1980). The amount of unreacted 1,1-dichloroethene remaining in the polymerized film is usually <10 ppm (Fishbein, 1979), but concentrations of 6.5-26.2 ppm have been detected in household and industrial film packaging (IARC, 1979; Fishbein, 1979). Even under severe conditions of packaging use, ≤10 ppb of the unreacted 1,1-dichloroethene is expected to migrate from the film into the food (Fishbein, 1979). Gilbert et al. (1980) monitored a variety of foodstuffs packaged in these films for the presence of 1,1-dichloroethene and found that levels in the foods were generally <5 ppb (with a maximum of 10 ppb) from films containing generally <1 ppm. Similar levels of 1,1-dichloroethene were found in British foods (Crosby, 1982). Based on these results, the maximum intake of 1,1-dichloroethene from the diet has been estimated to be 1 µg/person/day (Crosby, 1982). 1,1-Dichloroethene (levels not quantified) has been detected in beverages (Wallace et al., 1983).

trans-1,2-Dichloroethene has been detected in a sample of instant coffee at a level of 71-73 ppm (Kolb et al., 1984); this may be the result of solvent use during processing.

3.3. INHALATION

The dichloroethenes have been detected in ambient atmospheres throughout the United States; ambient air monitoring data for 1,1-dichloroethene and 1,2-dichloroethene are listed in Tables 3-3 and 3-4. The dichloroethenes are not emitted to the air by any known natural source (Singh et al., 1981); therefore, their presence in the ambient atmosphere is due to manmade sources (Singh et al., 1982). The major emission source of 1,1-dichloroethene has been reported to be the copolymer production of Saran® (Harkov et al., 1983). Other industrial emission sources of 1,1-dichloroethene include the production of ethylene dichloride and polyvinyl chloride and from coatings in textile manufacturing (Weant and McCormick, 1984). 1,1-Dichloroethene may also be emitted to the atmosphere from coal and fuel oil combustion sources (Cooke et al., 1984). 1,2-Dichloroethene is often manufactured as a by-product in the chlorination of various chlorinated compounds (Stevens, 1979); therefore, emissions from these processes is likely to be the major source of cis- and trans-1,2-dichloroethene. Since the dichloroethenes volatilize rapidly from water (see Section 2.1.5.), wastewaters containing these compounds may contribute measureable amounts to the atmosphere.

NIOSH (1978) has estimated that 58,000 workers are potentially exposed to 1,1-dichloroethene.

3.4. DERMAL

Pertinent dermal monitoring data could not be located in the available literature as cited in the Appendix.

TABLE 3-3

Air Monitoring Data for 1,1-Dichloroethene

Monitoring Location	Concentration (ppb)	Sampling Dates/Remarks	Reference
Rutherford, NJ	ND	46 samples	Harkov et al., 1981
Camden, NJ	ND	23 samples	
Newark, NJ	ND	50 samples	
South Amboy, NJ	0-0.01 (trace)	48 samples (one positive)	
Elizabeth, NJ	0-0.01 (trace)	54 samples (one positive)	
Newark, NJ	0.31-0.38 (mean)	58 samples (50 positive)	Harkov et al., 1984
Elizabeth, NJ	0.35-0.52 (mean)	63 samples (57 positive)	
Camden, NJ	0.36-1.02 (mean)	63 samples (59 positive)	
Pullman, WA	<0.005	December 1974-February 1975: rural atmosphere	Grimsrud and Rasmussen, 1975
Houston, TX	0.025 (average)	May, 1980	Singh et al., 1982
St. Louis, MO	0.009 (average)	May-June, 1980	
Denver, CO	0.031 (average)	June, 1980	
Riverside, CA	0.009 (average)	July, 1980	
Chicago, IL	0.022 (average)	April, 1981	
Los Angeles, CA	0.005 (mean)	April, 1979	Singh et al., 1981
Phoenix, AZ	0.030 (mean)	April-May, 1979	
Oakland, CA	0.013 (mean)	June-July, 1979	
West Germany	NA	gases originating from sanitary landfills	Bruckmann and Muelder, 1982
Edison, NJ	0.1 (trace)	Kin-Buc disposal site	Pellizzari, 1978
Tulsa, OK	0.1 (trace)	NC	
Houston, TX	0.1 (maximum)	NC	
Kanawha Valley, WV	<0.1	NC	
Front Royal, VA	0.1 (trace)	NC	
South Charleston, WV	<0.08	NC	
Birmingham, AL	<0.1	NC	
Baton Rouge, LA	<0.1	NC	
Upland, CA	<0.1	NC	
Magna, UT	<0.08	NC	
Grand Canyon, AZ	0.065 (trace)	NC	
Gelsmar, LA	0.05	NC	
Iberville Parish, LA	0.25 (maximum)	NC	
South Coast of California	ND	November, 1982-December, 1983	Shikiya et al., 1984

ND = Not detected; NA = not available; NC = no comment

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TABLE 3-4

Air Monitoring Data for 1,2-Dichloroethene

Monitoring Location	Concentration (ppb)	Sampling Dates/Remarks	Reference
Niagara Falls, NY	trace	1978 - air outside homes in Old Love Canal	Barkley et al., 1980
	15	1978 - air in a home basement at Love Canal	
Pullman, WA	<0.005	December, 1974 - February, 1975: rural atmosphere	Grimsrud and Rasmussen, 1975
Houston, TX	0.071 (mean)	May, 1980 - cis-isomer	Singh et al., 1983
St. Louis, MO	0.039 (mean)	May-June, 1980 - cis isomer	
Denver, CO	0.076 (mean)	June, 1980 - cis-isomer	
Riverside, CA	0.060 (mean)	July, 1980 - cis-isomer	
Staten Island, NY	0.018 (mean)	March-April, 1981 - cis-isomer	
Pittsburg, PA	0.013 (mean)	April, 1981 - cis-isomer	
Chicago, IL	0.019 (mean)	April-May, 1981 - cis-isomer	
Edison, NJ	1.3 (maximum)	Kin-Buc disposal site	Pellizzari, 1978
Tulsa, OK	<0.1	NC	
Kanawha Valley, WV	0.08 (trace)	NC	
Front Royal, VA	0.1 (trace)	NC	
South Charleston, WV	<0.08	NC	
Birmingham, AL	<0.1	NC	
Baton Rouge, LA	<0.1	NC	
Upland, CA	0.1 (trace)	NC	
Magna, UT	0.08 (trace)	NC	
Grand Canyon, AZ	0.065 (trace)	NC	
Geismar, LA	2.6 (maximum)	NC	
South Coast of California	NA	November, 1982-December, 1983	Shikiya et al., 1984

NA = Not available; NC = no comment

3.5. SUMMARY

The dichloroethenes have been detected in widespread samples of ambient water (see Tables 3-1 and 3-2) (Westrick et al., 1984) and ambient air (see Tables 3-3 and 3-4). These compounds may be emitted to environmental waters through industrial effluents, leaching (Sabel and Clark, 1984) and microbial degradation of 1,1,1-trichloroethane to yield dichloroethene (Smith and Dragun, 1985; Parsons et al., 1984). The major atmospheric emission source of 1,1-dichloroethene has been reported to be the copolymer production of Saran® (Harkov et al., 1983); additional sources include other industrial sources (Weant and McCormick, 1984), combustion sources (Cooke et al., 1984) and volatilization from contaminated waters. Foodstuffs packaged with Saran® film wrapping have been found to be contaminated by unreacted 1,1-dichloroethene remaining in the polymer film, although the concentrations found in the foods were small (Gilbert et al., 1980).

4. PHARMACOKINETICS

4.1. ABSORPTION

Gastrointestinal absorption of ^{14}C-1,1-dichloroethene by rats appears to be rapid and fairly complete, as indicated by excretion and body retention data following administration. Reichert et al. (1979) administered single gavage doses of ^{14}C-1,1-dichloroethene in tricaprylin of 0.5, 5.0 or 50.0 mg/kg to young adult female Wistar rats and measured the radioactivity in expired air, urine and feces, and remaining in the body after 72 hours. The recovery of 64.02-77.76% of the administered dose of radioactivity from expired air, urine and the body indicated substantial gastrointestinal absorption. Urinary excretion was 88-94% complete within 24 hours, indicating rapid gastrointestinal absorption. Similar results were obtained by Jones and Hathway (1978a) with young adult male Wistar rats. Following single gavage doses of ^{14}C-1,1-dichloroethene in corn oil of 0.5 or 350 mg/kg, 72-hour urinary and pulmonary excretion accounted for a total of 85.7-97.8% of the administered radioactivity at the low and high doses, respectively. Male Wistar rats may absorb 1,1-dichloroethene more efficiently than do female Wistar rats. Using young adult male Sprague-Dawley rats, McKenna et al. (1978) recovered 79-80% of the radioactivity from a 1 mg/kg dose of ^{14}C-1,1-dichloroethene in corn oil from expired air, urine and carcass within 72 hours, regardless of whether or not rats were fasted for 18 hours before treatment. In these experiments (Reichert et al., 1979; Jones and Hathway, 1978a; McKenna et al., 1978), fecal radioactivity accounted for 1.3-15.74% of the administered dose of radioactivity. Fecal radioactivity was determined to be associated with nonvolatile substances and was, therefore, assumed to represent metabolites of ^{14}C-1,1-dichloroethene suggesting that gastrointestinal absorption was virtually complete (Reichert et al., 1979).

Andersen et al. (1979) observed biphasic uptake of inhaled 1,1-dichloroethene (10-2000 ppm) by rats. The rapid phase, representing tissue equilibration, was a first-order process that was essentially complete in 60-80 minutes (concentration-independent rate constant of 2.2 hours^{-1}; half-life = 0.315 hours). The slow phase was associated with metabolism of 1,1-dichloroethene and continued for a varying time that depended upon the concentration of chemical and nutritional status of the animal.

Information regarding the absorption of cis- or trans-1,2-dichloroethene could not be located in the available literature as cited in the Appendix.

4.2. DISTRIBUTION

McKenna et al. (1978) intragastrically administered 1 or 50 mg ^{14}C-1,1-dichloroethene to rats and found that concentrations of radioactivity were highest in the liver and next highest in the kidneys after 72 hours. High concentrations of radioactivity also occurred in the kidneys and liver 30 minutes after intragastric administration of ^{14}C-1,1-dichloroethene (Jones and Hathway, 1978a). The radioactivity was more generally distributed throughout the soft tissues after 1 hour, but the liver and kidneys retained label longer than other tissues.

Jaeger et al. (1977) investigated the tissue distribution of radioactivity in rats 30 minutes after cessation of a 2-hour exposure to 2000 ppm ^{14}C-1,1-dichloroethene. The highest concentrations were found in the kidney and liver, with lesser amounts in the spleen, heart and brain. The radioactivity in the kidney was primarily water soluble (urinary metabolite), and ~1/3 of the hepatic radioactivity was bound to macromolecules. McKenna et al. (1978) exposed rats by inhalation to 10 or 200 ppm ^{14}C-1,1-dichloroethene for 6 hours and found that ~5-10% of the absorbed radioactivity was retained in the tissues, carcass and skin after 72 hours. All of

the radioactivity remaining in the animals after 72 hours was nonvolatile, indicating that the label was incorporated into nonvolatile metabolites. Concentrations of radioactivity were highest in the kidney and liver and decreased in the following order: kidney > liver > lung > skin and plasma > fat, muscle and remaining carcass. Accumulation was somewhat greater at the higher exposure level and in fasted (food deprivation for 18 hours) rats.

Information regarding the distribution of cis- or trans-1,2-dichloroethene could not be located in the available literature as cited in the Appendix.

4.3. METABOLISM

The metabolism of 1,1-dichloroethene has been characterized in animal studies and *in vitro* systems (U.S. EPA, 1985). 1,1-Dichloroethene is oxidized by mixed function oxidase enzyme systems to the epoxide 1,1-dichloroethylene oxide, which rearranges to chloroacetyl chloride. Chloroacetyl chloride undergoes further hydrolysis/dechlorination to form monochloroacetic acid, which can be oxidized to carbon dioxide or conjugated with glutathione. Glutathione conjugation initiates a series of transformation steps and can result in dithioglycolic acid, thioglycolyloxalic acid or N-acetyl-S-(carboxymethyl) cysteine. Chloroacetyl chloride can also conjugate with phosphatidyl ethanolamine and subsequently with methionine to form methylthio-acetylaminoethanol. The glutathione-derived mercapturic acids (N-acetyl cysteine derivatives) and thioglycolic acid conjugates are the primary urinary excretory products of 1,1-dichloroethene. The three primary oxidative metabolites of 1,1-dichloroethene (1,1-dichloroethylene oxide, chloroacetyl chloride and monochloroacetic acid) are reactive with nucleophilic groups on cellular macromolecules and are thus suggested as the ultimate cytotoxic and genotoxic metabolites of 1,1-dichloroethene.

Evidence is available that suggests that the metabolism of 1,1-dichloroethene is dose-dependent (Reichert et al., 1979; McKenna et al., 1978; Jones and Hathway, 1978a). Typical data were presented by Jones and Hathway (1978a) who measured pulmonary, urinary and fecal output of radioactivity in young adult male Wistar rats at 72 hours following single gavage doses of 0.5 or 350 mg/kg. Radioactivity in urine and feces, representing nonvolatile metabolites of 1,1-dichloroethene, declined from 80.2 and 8.3% of the dose at 0.5 mg/kg to 29.5 and 1.3% of the dose, respectively, at 350 mg/kg. Pulmonary excretion of $^{14}CO_2$ decreased from 4.8% of the dose at 0.5 mg/kg to 1.0% of the dose at 350 mg/kg, but exhalation of unaltered ^{14}C-1,1-dichloroethene increased from 0.7-67.3% of the dose at 0.5 and 350 mg/kg, respectively. The investigators did not indicate what steps in the metabolism of 1,1-dichloroethene were rate-limiting.

Evidence indicates that cis- and trans-1,2-dichloroethene are initially metabolized to the chloroethylene epoxides, which can rearrange to form 1,1-dichloroacetaldehyde (Henschler, 1977; Liebman and Ortiz, 1977). Dichloroacetaldehyde may also be produced by rearrangement of glycols formed by hydration from the epoxides. Bonse et al. (1975) demonstrated the production of small quantities of dichloroacetic acid and dichloroethanol in isolated rat liver perfused with either cis- or trans-1,2-dichloroethene. Acetone was expired by rats that inhaled 1,2-dichloroethene (Filser and Bolt, 1980; Filser et al., 1982).

Gas uptake studies indicated that the metabolism of trans-1,2-dichloroethene is dose-dependent (Filser and Bolt, 1979). The decline in concentration of trans-1,2-dichloroethene in the gas phase of a closed exposure system assumed first-order kinetics at lower concentratons and zero-order kinetics at higher concentrations.

4.4. EXCRETION

Excretion of 1,1-dichloroethene and its metabolites is rapid but influenced by dose. Intragastric administration of 0.5 mg/kg ^{14}C-1,1-dichloroethene to rats resulted in 71.3, 5.1, 0.6 and 3.9% (of dose) elimination of radioactivity in the urine, feces, exhaled 1,1-dichloroethene and exhaled CO_2 within 24 hours (Jones and Hathway, 1978a); the total amounts of radioactivity eliminated within 72 hours were 80.2, 8.3, 0.7 and 4.8%, respectively. With a 350 mg/kg dose, most of the radioactivity was expired as unchanged 1,1-dichloroethene; the percentages of administered radioactivity in the urine, feces, exhaled 1,1-dichloroethene and exhaled CO_2 were 17.6, 0.4, 62.4 and 0.3, respectively, after 24 hours and 1.3, 0, 67.3 and 29.5, respectively, after 72 hours. Similar dose-related shifts in the relative proportion of radioactivity excreted by various routes were reported by Reichert et al. (1979) for intragastric administration of 0.5, 5.0 and 50 mg/kg ^{14}C-1,1-dichloroethene to female rats and by McKenna et al. (1978) for intragastric administration of 1 and 50 mg/kg ^{14}C-1,1-dichloroethene to fed and fasted male rats.

Jones and Hathway (1978a) also demonstrated that biliary excretion and enterohepatic recirculation are important in the rat. These investigators measured the radioactivity collected for 48 hours in the urine of intact rats and in the urine and bile of rats with surgically fistulated bile ducts following an oral dose of ^{14}C-1,1-dichloroethene of 350 mg/kg. Intact rats excreted 21.8% of the dose of radioactivity in the urine, while bile duct-fistulated rats excreted 9.1% of the dose of radioactivity in the urine and 10.4% in the bile. These data suggest that biliary excretion is an important route of excretion for the metabolites of 1,1-dichloroethene. The

sum of biliary and urinary excretion in the bile duct-fistulated rat approximates the total urinary excretion in intact rats, suggesting that reabsorption of biliary metabolites was nearly complete. The reabsorbed metabolites were subsequently excreted in the urine.

Inhaled 1,1-dichloroethene is eliminated primarily through the urine. McKenna et al. (1977) exposed rats and mice to 10 ppm ^{14}C-1,1-dichloroethene for 6 hours and found that nearly all of the absorbed dose was eliminated by 72 hours. In rats, the percentage of the absorbed dose recovered in the urine, feces, exhaled air as 1,1-dichloroethene and exhaled air as CO_2 was 74.7, 9.7, 1.6 and 8.7, respectively. Residual radioactivity in the carcass represented ~4.8% of the absorbed dose. In mice, elimination through urine, feces, exhaled 1,1-dichloroethene and exhaled CO_2 was 80.8, 6.6, 0.7 and 4.6% of the absorbed dose with 5.5% remaining in the carcass.

Information regarding the elimination of cis- or trans-1,2-dichloroethene could not be located in the available literature as cited in the Appendix.

4.5. SUMMARY

Gastrointestinal absorption of 1,1-dichloroethene by rats appears to be rapid and relatively complete (McKenna et al., 1978; Jones and Hathway, 1978a; Reichert et al., 1979; Anderson et al., 1979). Pulmonary absorption appears to be biphasic with a rapid first-order phase independent of concentration representing tissue equilibration and the second slower concentration-dependent phase associated with metabolism (Anderson et al., 1979). Distribution of absorbed 1,1-dichloroethene throughout the body occurs rapidly, with the highest levels occurring in the liver and kidneys (McKenna et al., 1978; Jones and Hathway, 1978a; Jaeger et al., 1977). 1,1-Dichloroethene is metabolized in the liver with a number of possible reactive inter-

mediates, including an epoxide (1,1-dichloroethylene oxide), being formed (U.S. EPA, 1985). These reactive intermediates may react with macromolecules and are detoxified primarily by conjugation with glutathione. Elimination of metabolites and unmetabolized 1,1-dichloroethene occurs primarily through the urine, with up to 70-80% of the absorbed oral and inhalation doses excreted within 24 hours (Jones and Hathway, 1978a; Reichert et al., 1979; McKenna et al., 1978). Exhalation of unchanged 1,1-dichloroethene and CO_2 and fecal elimination can account for up to 10-15% of the absorbed dose, but at high doses/exposures much higher percentages are exhaled as unmetabolized 1,1-dichloroethene, suggesting that metabolism is rate-saturable. Biliary excretion accounts for a substantial proportion of administered compound, but metabolites excreted in the bile appear to be nearly completely reabsorbed and eventually excreted in the urine.

Information regarding the absorption, distribution or elimination of cis- or trans-1,2-dichloroethene could not be located in the available literature as cited in the Appendix. Limited evidence indicates that metabolism proceeds by epoxidation with rearrangement to form 1,1-dichloroacetaldehyde (Henschler, 1977; Liebman and Ortiz, 1977).

5. EFFECTS

5.1. CARCINOGENICITY

5.1.1. 1,1-Dichloroethene. The carcinogenicity of 1,1-dichloroethene was recently reviewed by U.S. EPA (1985). Carcinogenicity studies have been conducted in which rats, mice and hamsters were exposed by inhalation, gavage, incorporation in drinking water, subcutaneous injection and topical application. Positive responses were reported in an inhalation study (Maltoni et al., 1985) and in a skin initiation-promotion study (Van Duuren et al., 1979) with mice.

Maltoni et al. (1985) exposed groups of 30-120 male and female 9- or 16-week-old Swiss mice to 99.95% pure 1,1-dichloroethene in an inhalation chamber at concentrations of 0, 10 or 25 ppm, 4 hours/day, 4-5 days/week for 52 weeks (Table 5-1). Groups of mice were also exposed to 50, 100 or 200 ppm 1,1-dichloroethene for 4 hours/day, but treatment was discontinued after 1 week, 2 days and 2 days, respectively, because of acute toxic effects that included high mortality; therefore, 25 ppm represents a MTD. The mice were allowed to survive until spontaneous death or study week 121, at which time comprehensive histological examinations were conducted on all animals. Body weights were measured every 2 weeks during the treatment period and monthly thereafter.

A decrease in body weight occurred in the 9-week-old mice exposed to 25 ppm 1,1-dichloroethene, but treatment-related effects on survival were not evident in any of the 10 or 25 ppm groups (Maltoni et al., 1985). As detailed in Table 5-1, a significantly ($p<0.01$) increased incidence of kidney adenocarcinomas occurred in the 25 ppm males (28/119 in combined 25 ppm groups vs 0/196 in combined controls). A higher tumor incidence was seen in male mice started on treatment at age 9 weeks. Mammary carcinoma

TABLE 5-1

Inhalation Carcinogenicity Bioassay of 1,1-Dichloroethene with Swiss Mice[a]

Exposure[b] (ppm)	Duration of Treatment	No. at Start/ Sex[c]	Mice with Tumors: Kidney Adenocarcinomas				Mammary Tumors[f]				Pulmonary Adenomas[g]			
			Corrected Number[d]	No.	%	Average Latency Time[e] (weeks)	Corrected Number[d]	No.	%	Average Latency Time[e] (weeks)	Corrected Number[d]	No.	%	Average Latency Time[e] (weeks)
200	2 days	60(M)	1	0	NA	NA	6	0	NA	NA	5	0	NA	NA
		60(F)	28	0	NA	NA	53	1	1.9	87	46	1	2.2	57
		120(M,F)	29	0	NA	NA	59	1	1.7	87	53	1	1.9	57
100	2 days	30(M)	12	0	NA	NA	21	0	NA	NA	18	2	11.1	62±7
		30(F)	13	0	NA	NA	28	3	10.7	46±3	26	2	7.7	53±2
		60(M,F)	25	0	NA	NA	49	3	6.1	46±5	44	4	9.1	58±4
50	1 week	30(M)	17	1	5.9	64	27	0	NA	NA	26	1	3.8	62
		30(F)	14	0	NA	NA	28	2	7.1	39±13	27	3	11.1	80±8
		60(M,F)	31	1	3.2	64	55	2	3.6	39±13	53	4	7.5	75±7
25	52 weeks	30(M)	21	3[h]	14.3	71±5	29	0	NA	NA	28	7[j]	25.0	73±6
		30(F)	26	0	NA	NA	30	4	13.3	68±11	29	7[j]	24.1	85±6
		60(M,F)	47	3	6.4	71±5	59	4	6.8	68±11	57	14	24.6	30±4
25	52 weeks	120(M)	98	25[h]	25.5	75±2	117	1	0.8	46	113	16[j]	14.2	77±3
		120(F)	112	1	0.9	77	118	12	10.2	69±4	118	11[j]	9.3	78±6
		240(F)	210	26	12.4	75±2	235	13	5.5	67±4	231	27	11.7	77±3
10	52 weeks	30(M)	25	0	NA	NA	30	0	NA	NA	28	11[j]	39.3	71±5
		30(F)	26	0	NA	NA	30	6[i]	20.0	63±5	30	3[j]	16.0	68±4
		60(M,F)	51	0	NA	NA	60	6	10.0	63±5	58	14	24.1	70±4
0	NA	100(M)	56	0	NA	NA	92	1	1.1	25	80	3	3.7	66±7
		100(F)	73	0	NA	NA	97	2	2.1	49±7	92	4	4.3	56±4
		200(M,F)	129	0	NA	NA	189	3	1.6	41±9	172	7	4.1	60±4

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TABLE 5-1 (cont.)

Exposure[b] (ppm)	Duration of Treatment	No. at Start/ Sex[c]	Mice with Tumors: Kidney Adenocarcinomas — Corrected Number[d]	No.	%	Average Latency Time[e] (weeks)	Mammary Tumors[f] — Corrected Number[d]	No.	%	Average Latency Time[e] (weeks)	Pulmonary Adenomas[g] — Corrected Number[d]	No.	%	Average Latency Time[e] (weeks)
0	NA	90(M)	70	0	NA	NA	80	0	NA	NA	73	3	4.1	56±11
		90(F)	85	0	NA	NA	88	1	1.1	83	86	2	2.3	75±12
		180(M,F)	155	0	NA	NA	168	1	0.6	83	159	5	3.1	64± 8

[a]Source: U.S. EPA, 1985; Maltoni et al., 1985

[b]Exposures were 4 hours/day, 4-5 days/week.

[c]Animals were 16 weeks old at start except for 25 ppm groups with 120 per sex which were 9 weeks old at start.

[d]Live animals when the first tumor was observed: kidney adenocarcinoma, 55 weeks; mammary tumor, 27 weeks; pulmonary adenoma, 36 weeks. The percentages refer to the corrected numbers.

[e]Average time from the start of the experiment to the detection (at the periodic control or at autopsy).

[f]All mammary tumors in females were histologically diagnosed as carcinomas.

[g]Some pulmonary adenomas were cellular atypias.

[h]$p<0.01$, combined 25 ppm (28/119) males vs. combined control males (0/196) by chi-square test. Based on corrected numbers.

[i]$p<0.01$, combined control females (3/185) vs. 10 ppm females (6/30) and vs. combined 25 ppm females (15/148). Based on corrected numbers.

[j]$p<0.01$, combined control females (6/153) vs. 10 ppm females (11/?8) and vs. combined 25 ppm males (29/?94). Also, combined control females (6/178) vs. 10 ppm females (3/30) and vs. combined 25 ppm females (18/147).

NA = Not applicable

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incidences were significantly ($p<0.01$) increased in both the 10 ppm and combined 25 ppm female groups when compared with the combined controls, but the response was not dose-related (see Table 5-1). The incidence of pulmonary adenomas was significantly ($p<0.01$) increased in both the males and females exposed to 10 and 25 ppm (see Table 5-1), but the responses were not dose-related and pulmonary carcinomas were not observed. Maltoni et al. (1985) concluded that only the kidney tumors in the male mice were unequivocally related to treatment, particularly when considering the 0% spontaneous incidence of these tumors, and that this may be a strain-specific response. U.S. EPA (1985) noted that male mice of several strains are particularly sensitive to the toxic effects of 1,1-dichloroethene and that the kidney is a target organ for toxicity in mice.

Van Duuren et al. (1979) applied 121 mg 1,1-dichloroethene in acetone to the dorsal skin of 30 female Ha:ICR Swiss mice, followed 14 days later by 5 µg of phorbol myristate acetate in acetone 3 times weekly for life. A significant ($p<0.005$) increase in skin papillomas was observed (8/30 vs 0/30 in acetone-treated controls). Additionally, a squamous cell carcinoma was observed on one mouse in the control group but in none of the controls. The relevance of the positive results in this tumor initiation study is unclear, particularly since lifetime dermal application of 1,1-dichloroethene alone was not tumorigenic (Table 5-2).

Studies that do not indicate a carcinogenic effect of 1,1-dichloroethene are summarized in Table 5-2. Increased incidences of mammary tumors were observed in several treatment groups in two inhalation studies and a drinking water study with rats (Maltoni et al., 1985; Rampy et al., 1977; McKenna et al., 1982; Quast et al., 1983, 1986), but the occurrences were not considered to be treatment-related (see Table 5-2).

TABLE 5-2

Negative or Inconclusive Carcinogenicity Bioassays of 1,1-Dichloroethene

Route	Species, Strain	Number[a]/Sex	Dose or Exposure	Duration of Treatment	Duration of Study	Results	Reference
Inhalation	mouse, CD-1	16/M or F	0 or 55 ppm, 6 hours/day	5 days/week for 12 months	12 months	No significant increase in incidence of tumors; additional groups of four mice/sex sacrificed after 1, 2, 3, 6 and 9 months of treatment with similar results	Lee et al., 1977, 1978
Inhalation	mouse, CD-1	8 or 12/M or F	0 or 55 ppm, 6 hours/day	5 days/week for 1, 3 or 6 months	13, 15 or 18 months, respectively	No significant increase in incidence of tumors	Hong et al., 1981
Inhalation	rat, Sprague-Dawley	30/M or F (100/sex in controls)	0, 10, 25, 50 or 100 ppm, 4 hours/day	4-5 days/week for 52 weeks	137 weeks	Increased total number of rats with mammary tumors in 10 and 100 ppm groups and fibromas and fibroadenomas in all groups; no clear dose-response, latency time similar among groups, high (61%) incidence in controls and mammary carcinomas not increased	Maltoni et al., 1985
Inhalation	rat, Sprague-Dawley	30/M or F (60/sex in 100 ppm, 100/sex in controls)	0, 10, 25, 50, 100 or 150 ppm, 4 hours/day	4-5 days/week for 52 weeks	life	Incidences of brain tumors (gliomas, meningiomas or ependymomas) not significantly increased	Maltoni et al., 1982
Inhalation	rat, Sprague-Dawley	85-86/M or F	0, 25 or 75 ppm, 6 hours/day[b]	5 days/week for 18 months	24 months	Increased incidence of mammary adenocarcinomas at 25 ppm but not 75 ppm; not considered treatment-related	Rampy et al., 1977, 1978; McKenna et al., 1982; Quast et al.,1986
Inhalation	rat, Sprague-Dawley	16-30/M or F	0, 75 or 100 ppm, duration NR	NR	NR	Ongoing study; gross examination showed no significant increase in incidence of tumors	Viola and Caputo, 1977
Inhalation	rat, Wistar	30-51/M or F	0 or 200/100 ppm, 4 hours/day	5 days/week for 5 months (200 ppm) and subsequently 7 months (100 ppm)	20-22 months	No significant increase in incidence of tumors; extent of histological examinations not specified; limited report	Viola and Caputo, 1977

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TABLE 5-2 (cont.)

Route	Species, Strain	Number[a]/Sex	Dose or Exposure	Duration of Treatment	Duration of Study	Results	Reference
Inhalation	rat, CD	16/M or F	0 or 55 ppm, 6 hours/day	5 days/week for 12 months	12 months	No significant increase in incidence of tumors; additional groups of four rats/sex sacrificed after 1, 2, 3, 6 and 9 months of treatment with similar results	Lee et al., 1977, 1978
Inhalation	rat, CD	16/M or F	0 or 55 ppm, 6 hours/day	5 days/week for 10 months	22 months	No significant increase in incidence of tumors; additional groups of four or eight rats/sex were sacrificed after 1, 3 or 6 months of treatment and 12 months observation with similar results	Hong et al., 1981
Inhalation	hamster, Chinese	17-30/M or F	0 or 25 ppm, 4 hours/day	4-5 days/week for 52 weeks	157 weeks	No significant increase in incidence of tumors	Maltoni et al., 1985
Oral (gavage)	mouse, B6C3F1	50/M or F	0, 2 or 10 mg/kg/day in corn oil	5 days/week for 104 weeks	104 weeks	No significant increase in incidence of tumors with Bonferroni correction and life table analysis; increased incidence of adrenal pheochromocytomas, pancreatic islet-cell adenomas/carcinomas, testis interstitial-cell tumors and subcutaneous fibromas in males and pituitary adenomas in females indicated without the statistical corrections	NTP, 1982
Oral (gavage)	rat, F344	50/M or F	0, 1 or 5 mg/kg/day in corn oil	5 days/week for 104 weeks	104 weeks	No significant increase in incidence of tumors with Bonferroni correction and life table analysis; significantly increased incidence of lymphomas in female mice without the statistical corrections	NTP, 1982
Oral (drinking water)	rat, Sprague-Dawley	48/M or F (80/sex in controls)	0, 7, 10 or 20 mg/kg/day (males) 0, 9, 14 or 30 mg/kg/day (females)	2 years	2 years	Increased incidence of mammary gland fibroadenomas/adenofibromas in low dose but no dose-response, high incidence in controls, low dose incidence in range of historical controls; mammary carcinomas not increased; increased incidence of total tumors in males	Rampy et al., 1977, 1978; Humiston et al., 1978; Quast et al., 1983 U.S. EPA, 1985

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TABLE 5-2 (cont.)

Route	Species, Strain	Number[a]/Sex	Dose or Exposure	Duration of Treatment	Duration of Study	Results	Reference
Oral (gavage)	rat, Sprague-Dawley	50/M or F (100/sex controls)	0, 5, 10 or 20 mg/kg/day in olive oil	4-5 days/week for 52 weeks	147 weeks	No significant increase in incidence of tumors	Maltoni et al., 1985
Oral (gavage)	rat, Sprague-Dawley	50/M or F (82 M and 77 F in controls)	0 or 0.5 mg/kg/day in olive oil	4-5 days/week for 52 weeks	147 weeks	No significant increase in incidence of tumors	Maltoni et al., 1985
Oral	rat, Sprague-Dawley	50/M or F (175/sex in controls)	0, 0.5, 5, 10 or 20 mg/kg/day in olive oil	4-5 days/week for 52-59 weeks	52-59 weeks	Incidences of brain tumors (gliomas, meningiomas or ependymomas) not significantly increased	Maltoni et al., 1982
Oral (gavage)	rat, BDN	64-90/M or F	0 or 150 mg/kg in olive oil on maternal day 17 of gestation; from weaning, 0 or 50 mg/kg in olive oil	1 day/week for 120 weeks	120 weeks	No significant increase in incidence of tumors; increased prevalence of hyperplastic nodules in liver	Ponomarkov and Tomatis, 1980
Skin	mouse, Ha: ICR Swiss	30/F	0, 40 or 121 mg in acetone	3 applications/ week for life	life	No local papillomas or carcinomas or significant increase in incidence of distant tumors	Van Duuren et al., 1979
Subcutaneous injection	mouse, Ha: ICR Swiss	30/F	0 or 2 mg in trioctanoin	once weekly for 548 days	548 days	No local (flank) sarcomas or significant increases in incidence of distant tumors	Van Duuren et al., 1979

[a]Numbers in each treated and control group unless indicated otherwise

[b]Rats in the 25 and 75 ppm groups were exposed to 10 and 40 ppm, respectively, for the first 42 days of exposure

NR = Not reported

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Limited information is available regarding the carcinogenic potential of 1,1-dichloroethene to humans. Ott et al. (1976) conducted a retrospective mortality study of a small cohort of 138 chemical company workers exposed primarily to 1,1-dichloroethene (<0.2% vinyl chloride contaminant). Cumulative career dosages, determined by multiplying TWA exposure estimates times duration (months) of potential exposure, indicated that 50, 28, 28 and 32 of the workers were exposed to <500, 500-999, 1000-1999 and ≥2000 ppm, respectively. Thirty-five, 43, 35 and 25 of the workers were exposed for <12, 12-59, 60-119 and ≥120 months, respectively. Approximately 40% (55/138) of the workers had <15 years latency since the first exposure. Among the 138 workers, only five deaths were reported (7.5 expected) and only one was due to cancer (respiratory cancer; 0.3 expected, a nonsignificant difference). The small numbers of subjects in this study (particularly with lengthy duration of exposure) and limited latency period preclude interpretation of noncarcinogenicity.

5.1.2. 1,2-Dichloroethene. Information regarding the carcinogenicity of cis- or trans-1,2-dichloroethene or mixtures of these isomers could not be located in the available literature as cited in the Appendix. Both isomers and an unspecified mixture of isomers have been scheduled for testing by the National Toxicology Program (NTP, 1985).

5.2. MUTAGENICITY

5.2.1. 1,1-Dichloroethene. Numerous studies indicate that 1,1-dichloroethene is mutagenic to many strains of Salmonella typhimurium, including TA1530, TA1535, TA1538, TA98 and/or TA100 (Bartsch et al., 1975, 1979; Oesch et al., 1983; McCarroll et al., 1983; Jones and Hathway, 1978b; Cerna and Kypenova, 1977; Baden et al., 1976, 1977, 1978; Simmon et al., 1977; Malaveille et al., 1977; Waskell, 1978). 1,1-Dichloroethene is often used

as a positive control in studies determining the mutagenicity of gaseous chemicals. Although vapor exposure was the most commonly used method in these studies, a variety of other exposure conditions were also used (e.g., plate incorporation, liquid suspension, host-mediation). 1,1-Dichloroethene also produced reverse mutations in E. coli WP2uvrA (Jones and Hathway, 1978b) and reverse mutation of the arg^+ loci in E. coli K12 (Greim et al., 1975). Metabolic activation was necessary to produce a mutagenic response in all of these bacterial assays. Mutagenicity assays performed in liquid media and the host-mediated assay with mice using the yeast Saccharomyces cerevisiae D7 were positive for both point mutations and mitotic gene conversion (Bronzetti et al., 1981).

Negative results were obtained in mutagenicity assays using V79 Chinese hamster cells in culture in which the endpoint was resistant to 8-azoquanine and ouabain (Drevon and Kuroki, 1979), and in dominant lethal assays conducted with CD-1 mice (Anderson et al., 1977) and CD rats (Short et al., 1977a) exposed by inhalation. Single or five daily intraperitoneal injections of 1,1-dichloroethene at one-half or one-sixth the LD_{50}, respectively, did not produce chromosomal aberrations in bone marrow cells of mice (Cerna and Kypenova, 1977). Exposures to high concentrations (7%) of 1,1-dichloroethene vapor for 24 hours induced SCEs in cultured Chinese hamster ovary cells (McCarroll et al., 1983).

5.2.2. 1,2-Dichloroethene. cis-1,2-Dichloroethene and trans-1,2-dichloroethene were not mutagenic in spot tests with Salmonella typhimurium strains TA1950, TA1951, TA1952, TA1535, TA1538, TA100 or TA98 when tested without a metabolic activation system (Cerna and Kypenova, 1977). cis-1,2-Dichloroethene was mutagenic in S. typhimurium strains TA1950, TA1951 and TA1952 when tested in host-mediated assays with an unspecified species, but

the trans-isomer was not mutagenic in the same strains (Cerna and Kypenova, 1977). Trans- or cis-1,2-dichloroethene did not produce forward mutation to 5-methyltryptophan resistance or reverse mutation at the gal^+, arg^+ or nad^+ loci in E. coli K12 (Greim et al., 1975).

cis-1,2-Dichloroethene and trans-1,2-dichloroethene were not mutagenic (not elaborated) in S. cerevisiae D7 in suspension assays with or without metabolic activation preparations (Bronzetti et al., 1984). The cis-isomer reportedly showed evidence of mutagenicity in S. cerevisiae D7 in an unspecified in vivo intrasanguineous host-mediated assay (significant increases in convertants at the trp locies and revertants at the ilv locies), but mutagenic activity was not demonstrated with the trans-isomer (Bronzetti et al., 1984).

Five daily intraperitoneal injections of cis-1,2-dichloroethene at one-sixth the LD_{50} produced a significant increase in the number of chromosome aberrations in bone marrow cells of mice (Cerna and Kypenova, 1977). Similar treatment with the trans-isomer or single intraperitoneal injections of cis- or trans-1,2-dichloroethene at one-half the LD_{50} were not clastogenic.

5.3. TERATOGENICITY

5.3.1. 1,1-Dichloroethene. Portions of this section are taken from a U.S. EPA (1983a) review of 1,1-dichloroethene.

Murray et al. (1979) administered 200 ppm (200 mg/ℓ) 1,1-dichloroethene in the drinking water to 26 Sprague-Dawley rats on days 6-15 of gestation. A group of 24 bred rats served as controls. It was determined that the treated dams consumed ~40 mg/kg/day 1,1-dichloroethene. No maternal toxicity was observed, and no significant differences were seen in numbers of litters, implantation sites/dam, live fetuses/litter, resorptions/litter, fetal sex ratios, fetal body weights or fetal malformations

between exposed and control dams. There were significantly more corpora lutea/dam in treated animals, but this was not considered treatment-related because the number of corpora lutea is established before day 6 of gestation. The only other significant difference was an increase in fetal length in the exposed group.

Murray et al. (1979) also investigated the effects of 1,1-dichloroethene inhalation on embryonic and fetal development in Sprague-Dawley rats and New Zealand rabbits. Rats were exposed to concentrations of 20 ppm (80 mg/m^3) (44 rats), 80 ppm (320 mg/m^3) (30 rats) or 160 ppm (630 mg/m^3) (30 rats) 1,1-dichloroethene for 7 hours/day on days 6-15 of gestation. Concurrent controls (20-47/dose) breathed filtered air. Maternal effects in rats included decreased food consumption and weight gain changes at 160 and 80 ppm and increased liver weight at the 160 ppm level. These effects were not significant for the 20 ppm group. Compared with controls, no significant differences were observed in treated groups at any level with respect to numbers of litters, corpora lutea/dam, implantation sites/dam, live fetuses/litter, resorptions/litter, fetal sex ratio, fetal body weights and fetal length. Significant differences ($p<0.05$) were seen in skeletal alterations in fetuses of the 80 and 160 ppm exposed dams when compared with controls, including delayed ossification of skull and centra of cervical vertebrae and wavy rib formation.

Rabbits were exposed to 0 ppm (16 rabbits), 80 ppm (320 mg/m^3) (22 rabbits) or 160 ppm (630 mg/m^3) (18 rabbits) for 7 hours/day on days 6-15 of gestation (Murray et al., 1979). Maternal deaths occurred in all groups including controls but were not related to 1,1-dichloroethene exposure. Body weight changes were significant at both exposure levels when compared with controls, and significantly increased liver weights were seen in dams

exposed to 80 ppm. No significant differences were seen in numbers of litters, corpora lutea/dam, implantation sites/dam, live fetuses/litter, fetal sex ratios, fetal body weight or fetal length. At the 160 ppm level, the number of resorptions/litter was significantly greater than in control dams, but this may have been due to maternal toxicity rather than to a direct effect on the embryo. No significantly different fetal abnormalities were seen at either exposure level when compared with controls.

Short et al. (1977b) exposed CD rats and CD-1 mice by inhalation to 0, 15, 57, 300 or 449 ppm (0, 59, 230, 1190 or 1780 mg/m^3) 1,1-dichloroethene and 0, 15, 30, 57, 144 or 300 ppm (0, 59, 120, 230, 571 or 1190 mg/m^3) 1,1-dichloroethene, respectively, for 23 hours/day on days 6-16 of gestation. There were ~20 animals in the exposed groups and 60 in the control groups. The rats and mice were sacrificed on gestation days 20 and 17, respectively. In rats, an appreciable number of maternal deaths (25%) occurred at 300 and 449 ppm, and food consumption and weight gain was decreased at $\geq$15 ppm. Similar effects occurred in mice, with 100% maternal mortality at 144 or 300 ppm and reduced food consumption and weight gain in all groups except the 15 ppm group. Early resorptions were common in all exposed groups with 100% resorption in mice exposed to 30 and 57 ppm and 49 and 64% resorptions in rats exposed to 57 and 449 ppm, respectively. Gross external abnormalities were not seen in surviving pups of either species. Some soft-tissue anomalies were observed in rats at 15 and 57 ppm, but incidences were not statistically significant. Significantly increased incidences of incomplete ossification of sternebrae occurred in mice at the 15 ppm level and in rats at the 15, 57 and 300 ppm levels. Since interpretation of these effects is complicated by the maternal toxicity, another study was conducted with shorter exposures in mice (Short et al., 1977b).

1,1-Dichloroethene was administered for 23 hours/day on gestation days 6-15 (54 ppm; 210 mg/m³), 8-15 (41, 54 and 74 ppm; 16, 210 and 290 mg/m³), 10-15 (54 ppm; 210 mg/m³), 12-15 (54 ppm; 210 mg/m³), 6-9 (56, 81 and 112 ppm; 220, 320 and 444 mg/m³), 9-12 (56, 81 and 112 ppm), 12-15 (56, 81 and 112 ppm) and 15-17 (56, 81 and 112 ppm). Incidences of resorption were decreased by the shortened exposure periods, but the weight loss in treated dams was still evident. Significantly increased incidences of cleft palate occurred at the 54 ppm level from gestation days 10-15 and 12-15. Other abnormalities included ossification problems as described above and immature skin and hematomas. Interpretation of these results is complicated because some of these anomalies were also observed in some groups of animals that served as diet-restricted controls and because maternal toxicity occurred at nearly all concentrations of 1,1-dichloroethene used.

A multiple generation reproduction study was conducted in which Sprague-Dawley rats were provided drinking water containing 0, 50, 100 or 200 ppm (0-200 mg/ℓ) 1,1-dichloroethene (Section 5.4.) (Nitschke et al., 1980, 1983). Treatment-related effects on fetal survival, litter size, growth rates or weanling development did not occur in any dose group or generation.

5.3.2. 1,2-Dichloroethene. Information regarding the teratogenicity of cis- or trans-1,2-dichloroethene or mixtures of these isomers could not be located in the available literature as cited in the Appendix.

5.4. OTHER REPRODUCTIVE EFFECTS

5.4.1. 1,1-Dichloroethene. Portions of this section are taken from a U.S. EPA (1983a) review of 1,1-dichloroethene.

A 3-generation reproduction study was conducted by Nitschke et al. (1980) in which Sprague-Dawley rats were maintained on drinking water containing 0, 50, 100 or 200 ppm (0-200 mg/ℓ) 1,1-dichloroethene. The

parental generation (F_0) consisted of 15 males and 30 females in the control group and 10 males and 20 females in each of the three treatment groups. After 100 days of exposure, the F_0 males and F_0 females were mated (within dose groups) to produce the first filial (F_{1a}) generation. Because of low fertility during the initial breeding, the F_0 rats were re-mated after a period of $\geq$10 days after F_{1a} weaning to produce F_{1b} offspring. The F_{1a} and F_{1b} litters of all dose groups were examined for reproductive indices (number of litters/number of dams; survival of pups at 1, 7, 14 and 21 days). The rats to be raised as the F_1 generation adults were randomly selected from the F_{1b} generation and exposure to 1,1-dichloroethene was continued. All other F_{1a} and F_{1b} rats were sacrificed at 21-24 days of age for internal and external examinations. At ~110 days of age, the F_{1b} adults were mated, producing the F_2 progeny. The F_2 litters were examined similarly to the previous litters, and randomly selected males and females were maintained for F_2 adults. The remaining F_2 weanlings were killed and examined for external and internal abnormalities. Adult F_2 rats were mated at ~110 days of age to produce the F_{3a} generation. Because survival of the F_{3a} litters in all groups receiving 1,1-dichloroethene was decreased, the F_2 adults were re-mated after the F_{3a} litters were weaned. To determine if the decreased survival in the dose groups was due to prenatal or postnatal exposure to 1,1-dichloroethene, one-third of the F_{3b} litters born to 200 ppm 1,1-dichloroethene-treated dams were exchanged with litters of untreated dams. No dose-related decreased survival was noted in any groups of the F_{3b} litter. At least 10 days after the F_{3b} litters were weaned, the F_2 parents were mated again to produce the F_{3c} litters to determine survival rates of this group. A selected number of male and female rats from each dose group of the F_{3b}

litters were raised for 185-213 days as F_3 adults. All remaining weanling rats of the F_{3a}, F_{3b} and F_{3c} litters were sacrificed at 21-24 days of age for external and internal examination (Nitschke et al., 1980).

The results of this study indicate few, if any, dose-related effects on reproduction or the development of progeny in rats treated with 1,1-dichloroethene in the drinking water at the dose levels tested (Nitschke et al., 1980). A slight decrease in the fertility (number of litters/number of mated dams) of the F_0 rats was noted in controls and the two highest dose groups (120 and 200 ppm) when compared with historical controls of Sprague-Dawley rats. Survival of F_2 progeny was decreased in all treated groups but this response was not dose-related since mortality was highest in the 100 ppm group and similar at 50 and 200 ppm. Decreased survival during the lactation period in the F_{3a} generation did appear to be dose-related, but survival in the F_{3b} litters of dams given 100 and 200 ppm 1,1-dichloroethene was higher than controls. It was not possible to ascertain if the decreased survival in the F_{3a} generation rats was due to prenatal or postnatal exposure to 1,1-dichloroethene. Decreased survival in any group of the F_{3b} generation, including those cross-fostered, was not noted. The decreased survival of the F_{3a} generation is questionable since the similarly treated F_{3c} generation showed no dose-related decreased survival.

Fetal survival, litter size, and growth rates of the neonates showed no consistent dose-related effects for any generation during this study (Nitschke et al., 1980). At necropsy, histopathological examination of the liver and kidneys revealed hepatocellular fatty changes and pronounced hepatic lobular patterns in adult F_1 rats treated with 100 or 200 ppm 1,1-dichloroethene. Fatty changes of the hepatocytes were also noted in adult F_2 females. Liver degeneration was noted in F_1 adults treated

with 100 or 200 ppm 1,1-dichloroethene and at all dose levels in F_2 adults. No dose-related malformations or changes in organ weights were revealed after necropsy of weanlings in any dose group or generation.

The 3-generation study by Nitschke et al. (1980) indicated that 1,1-dichloroethene in drinking water at 50, 100 or 200 ppm did not adversely affect reproduction or neonatal development in rats. Neonatal survival was decreased in the F_{3a} litters, but contradictory results were shown in the F_{3b} and F_{3c} litters. Histopathological examination revealed mild dose-related hepatotoxic effects in treated adult rats, but no dose-related changes or malformations were seen in neonates. Reproductive capacities in adults did not appear to be altered by 1,1-dichloroethene exposure.

5.4.2. 1,2-Dichloroethene. Pertinent data regarding reproductive effects of cis- or trans-1,2-dichloroetnene or mixtures of these isomers could not be located in the available literature as cited in the Appendix.

5.5. CHRONIC AND SUBCHRONIC TOXICITY

5.5.1. 1,1-Dichloroethene. Portions of this section are taken from U.S. EPA (1983a, 1985) reviews of 1,1-dichloroethene.

NTP (1982) conducted a carcinogenesis bioassay in which groups of 50 F344/N rats of each sex were administered 0, 1 or 5 mg/kg/day 1,1-dichloroethene in corn oil by gavage 5 days/week for 104 weeks. Groups of 50 B6C3F1/N mice of each sex were similarly treated with dosages of 0, 2 or 10 mg/kg/day. Mortality and growth rates in rats or mice were not affected by 1,1-dichloroethene administration. 1,1-Dichloroethene was not carcinogenic under the conditions of the bioassay (see Section 5.1.1.), but several non-neoplastic lesions were observed. In rats, the incidences of chronic renal inflammation were 43/48 in high-dose males, 24/48 in low-dose males, 26/50 in control males, 9/44 in high-dose females, 6/49 in low-dose females and

3/49 in control females. The incidences of liver necrosis (focal, multifocal and diffuse) in mice were 7/49 in high-dose males, 3/46 in low-dose males, 1/46 in control males, 1/49 in high-dose females, 4/49 in low-dose females and 0/49 in control females. It was stated that the increased incidence of these lesions at high doses of 1,1-dichloroethene may have been related to the administration of the chemical (NTP, 1982).

Rampy et al. (1977, 1978), Humiston et al. (1978) and Quast et al. (1983) conducted a chronic toxicity/oncogenicity study of 1,1-dichloroethene in which groups of 48 Sprague-Dawley rats of each sex were exposed to 50, 100 or 200 ppm 1,1-dichloroethene (nominal concentrations) in the drinking water for $\leq$2 years. Eighty rats of each sex served as untreated controls. Based on mean analyzed concentration in the drinking water, the rats were determined to have ingested 0, 7, 10 or 20 mg/kg/day (males) and 0, 9, 14 or 30 mg/kg/day (females). Statistically significant increased mortality occurred in some treated groups at various times during the study, but the increases were not dose-related or consistent, and were not considered to be treatment-related. No significant differences in body weights, food consumption or water consumption were observed in treated rats when compared with controls. Hematological indices, urinalyses and clinical chemistry parameters were unaffected by the treatment. Comprehensive histological examinations that were performed on all surviving rats after 2 years showed increased incidences of hepatic lesions, which included hepatocellular fatty changes and periportal hepatocellular hypertrophy at all exposure levels, in treated females and in 200 ppm males, and centrilobular atrophy in 200 ppm treated females. Treatment-related hepatocellular necrosis was not observed.

Groups of 10 rats of each sex were also exposed to the same concentrations of 1,1-dichloroethene in the drinking water in a concurrent 90-day

study (Rampy et al., 1977). Rats treated at the 200 ppm level had an increased incidence of cytoplasmic vacuolization of hepatocytes, which was considered a minimal reversible effect.

Hepatic effects of chronic oral treatment in rats were also reported by Ponomarkov and Tomatis (1980). In this study, a single dose of 0 or 150 mg/kg 1,1-dichloroethene in olive oil was administered by gavage to 14 or 24 pregnant BDIV rats, respectively, on day 17 of gestation. The progeny, beginning at weaning, were then given weekly doses of 0 mg/kg (53 males, 53 females) or 50 mg/kg (81 males, 64 females) by gavage for 120 weeks. No differences were seen in litter size, preweaning mortality, postweaning mortality or body weights between exposed and control groups. Lung and kidney congestion were seen in some treated rats that died after 30 weeks of exposure. Hemorrhages, multiple lobular liver necroses and degenerative liver parenchymal cells were observed in treated rats that died at 80-90 weeks and in 120-week survivors.

Maltoni et al. (1985) administered 1,1-dichloroethene in corn oil to groups of 50 Sprague-Dawley rats of each sex by gavage at concentrations of 5, 10 or 20 mg/kg/day, 4-5 days/week for 52 weeks. Control groups of 100 rats of each sex were similarly exposed to the vehicle. Additional groups of rats were exposed to 0 (82 males, 77 females) or 0.5 mg/kg/day 1,1-dichloroethene by gavage according to the same 52-week schedule in a related experiment. Both studies were terminated after 95 weeks of observation. Treatment-related effects on body weight, survival, clinical signs and gross or microscopic tissue pathology were not indicated in either study.

Groups of four beagle dogs of each sex were administered 1,1-dichloroethene in peanut oil by capsule daily at doses of 0, 6.25, 12.5 or 25 mg/kg for 97 days (Quast et al., 1983). Differences in general appearance or

demeanor, body weight, food consumption, hematological and clinical chemistry indices, urinalysis, organ weights and gross and microscopic appearance of the tissues were not observed between the treated and control animals.

An inhalation study was conducted in which groups of 104 Sprague-Dawley rats of each sex were exposed to 1,1-dichloroethene, 6 hours/day, 5 days/week for 18 months (Rampy et al., 1977; McKenna et al., 1982; Quast et al., 1986). The exposure levels were 0, 10 or 40 ppm (0, 40 or 160 mg/m^3) for the first 42 days of exposure and 0, 25 and 75 ppm (0, 100 and 300 mg/m^3), respectively, for the remainder of the exposure period. The rats were observed for an additional 6 months after termination of exposure, but the group sizes during the 2-year portion of the study were 85-86, which was due to interim sacrifices that were conducted after 6, 12 and 18 months of exposure. Statistically significant increases in mortality and changes in body weights (decreases in males, increases in females) occurred at various times during the study, but these effects were not dose-related or statistically significant and therefore not attributed to 1,1-dichloroethene exposure. Comprehensive hematology determinations and urinalyses performed on 5 or 10 rats/sex/level at interim sacrifices or 8-19 rats/sex/level at the terminal sacrifice also did not reveal any consistent effects that were treatment-related. Organ weight determinations on 5 rats/sex/level at the 6- and 12-month interim sacrifices and on 8-21 rats/sex/level at the terminal sacrifice showed significantly decreased liver weights in treated males and significantly increased kidney weights in treated females at 12 months; these changes were not observed at the other interim kills or at termination. Comprehensive histological examinations showed that the only treatment-related effect was minimal midzonal hepatocellular fatty change in males and females as early as the 6-month interim sacrifice. This lesion

did not progress in severity by the 12-month interim sacrifice. No unusual incidence of fatty changes occurred in moribund or dead males during the 18-month exposure, in moribund or dead males or females during the 6-month postexposure period, or in males or females at the 24-month terminal sacrifice. This reversible hepatic effect was also found during a separate 90-day inhalation study in which groups of 20 rats/sex were exposed to 0, 25 or 75 ppm 1,1-dichloroethene (Rampy et al., 1977); in this study, 8 and 12 rats/sex/dose were sacrificed after 30 and 90 days, respectively.

Lee et al. (1977, 1978) exposed CD-1 mice and CD-rats to 55 ppm (220 mg/m³) 1,1-dichloroethene vapor, 6 hours/day, 5 days/week for ≤1 year. Each experimental group was composed of 36 males and 36 females per species. Control groups were of the same composition and were exposed to uncontaminated air on the same schedule. Two male mice died on the 13th day of exposure and had acute toxic hepatitis and tubular necrosis of the renal cortex. Various hepatic lesions occurred in treated mice, including enlarged and basophilic hepatocytes, enlarged nuclei with eosinophilic inclusions, mitotic figures or polyploidy, microfoci of mononuclear cells, focal degeneration and necrosis. Rats of both sexes exposed to 1,1-dichloroethene had reduced body weights, compared with controls, and hepatocellular fatty changes.

Hong et al. (1981) exposed 12 male and 12 female CD-1 mice and 18 male and 18 female CD rats to 0 or 55 ppm (220 mg/m³) 1,1-dichloroethene vapor, 6 hours/day, 5 days/week for 6 months (mice) or 10 months (rats) and observed both species for 12 months after termination of treatment. Of the mice treated for 6 months, 11/24 died or were killed when moribund during the observation period as compared with 11/56 control mice. Twenty of 30 rats exposed for 10 months died or were killed when moribund during the

observation period as compared with 13/32 controls. Specific causes were not indicated for the deaths, but tumor incidences did not significantly differ between the exposed and unexposed animals.

Maltoni et al. (1985) exposed Sprague-Dawley rats, Swiss mice and Chinese hamsters to 1,1-dichloroethene vapor, 4 hours/day, 4-5 days/week for 12 months in carcinogenicity bioassays. Groups of thirty 16-week-old animals/sex were exposed to concentrations of 10, 25, 50 or 100 ppm (40, 100, 200 or 400 mg/m^3) and observed for 85 weeks; control groups consisted of 100 rats/sex. Groups of thirty 16-week-old mice/sex were exposed to 10 or 25 ppm 1,1-dichloroethene and observed for 69 weeks; 100 mice/sex served as controls. Groups of 90 and 120 nine-week-old mice/sex were also exposed to 0 and 25 ppm 1,1-dichloroethene and observed for 69 weeks in the same experiment. The hamsters were exposed to 0 ppm (18 males, 17 females) or 25 ppm (30/sex) 1,1-dichloroethene and observed for 105 weeks. Treatment-related effects that were limited to the hamsters included excess mortality (males only) and adenomatous hyperplasia of the respiratory epithelia primarily in the males. A decrease in body weight was reported in the 9-week-old mice that were exposed to 25 ppm 1,1-dichloroethene, but carcinogenesis (kidney adenocarcinomas) was also evident in these animals. Detailed results regarding survival, body weight and general pathology in the animals in this study were reported in an Appendix that was not included with the copy of the report available to the authors of this document.

Prendergast et al. (1967) exposed several species of animals to 90-day continuous inhalation exposures of 0, 20, 61, 101 or 189 mg/m^3 1,1-dichloroethene. Treatment groups contained 15 Long-Evans or Sprague-Dawley rats, 15 Hartley guinea pigs, 3 or 9 squirrel monkeys, 2 beagle dogs and 3 New Zealand rabbits (101 mg/m^3 only). Control groups consisted of 304

rats, 314 guinea pigs, 57 monkeys, 34 dogs and 48 rabbits. Early mortality was observed in guinea pigs and monkeys at all exposure levels without visible signs of toxicity in survivors, when compared with controls. Nonspecific inflammatory changes were found in the lungs of all species at all dose levels and were not due to 1,1-dichloroethene exposure. Weight changes were observed at all levels, but only the 189 mg/m³ exposure resulted in definite depression of growth in all species. The high level of exposure also resulted in elevated liver alkaline phosphatase and serum glutamic-pyruvic transaminase activities in rats and guinea pigs. Definite liver and kidney lesions were observed in dogs, monkeys and rats only at the 189 mg/m³ level. The liver lesions included fatty metamorphoses, focal necrosis, hemosiderin deposition, lymphocytic infiltration, bile duct proliferation, fibrosis and pseudo-lobule formation. Rats had nuclear hypertrophy of the renal tubule epithelium when exposed to 189 mg/m³ 1,1-dichloroethene.

5.5.2. 1,2-Dichloroethene. Freundt et al. (1977) conducted a subchronic inhalation study of trans-1,2-dichloroethene, in which groups of six female SPF Wistar rats were exposed to 0 or 200 ppm (0 or 800 mg/m³) concentrations, 8 hours/day, 5 days/week for 1, 2, 8 or 16 weeks. Immediately following the last exposure, gross pathological examinations were conducted and lung, heart, liver, kidney, spleen, brain, muscle and sciatic nerve sections were taken for histological examination. Fatty accumulation in the liver (lobules and Kupffer cells) occurred in some of the treated rats in each of the exposure groups, and the incidence was related to length of exposure; after 16 weeks of exposure 3/6 rats developed severe fatty changes. Slight fat accumulation was also reported in 2/6 control rats.

Lung damage (capilliary hyperemia and alveolar septum distention) occurred in all of the treated rats, and half of the rats in the 8- and 16-week studies also exhibited severe pneumonic infiltration. These effects did not occur in any of the control rats. There were no signs of central nervous system depression in any of the treated rats.

The data reported by Freundt et al. (1977) appeared to be inconsistent with unpublished data reported by Torkelson (1965) to the ACGIH (1980), which indicate that exposure to 500 or 1000 ppm (2000 or 4000 mg/m³) 1,2-dichloroethene vapor, 7 hours/day, 5 days/week for 6 months did not produce effects in rats, rabbits, guinea pigs or dogs. The parameters studied were growth, mortality, organ and body weights, hematology, clinical chemistry and gross and microscopic pathology. The isomer used in this study was not specified in ACGIH (1980), but Torkelson and Rowe (1981) reported that exposure was to a mixture of 60% cis- and 40% trans-isomers. The 1000 ppm group, therefore, was exposed to a minimum of 400 ppm of trans-1,2-dichloroethene, a concentration that is higher than the 200 ppm adverse effect level for trans-1,2-dichloroethene level in the Freundt et al. (1977) study.

5.6. OTHER RELEVANT INFORMATION

An acute oral LD_{50} of 2500 mg/kg was determined for male rats fed a corn oil solution of 1,1-dichloroethene (Jenkins et al., 1972). Four-hour LC_{50}s of 6350 ppm (25,200 mg/m³) (Siegel et al., 1971) and 32,000 ppm (130 g/m³) (Carpenter et al., 1949) have been reported for rats. The liver and kidneys are target organs for 1,1-dichloroethene toxicity regardless of the route of administration or duration of exposure (U.S. EPA, 1985).

Central nervous system depression (i.e., narcosis), rather than liver and kidney injury, appears to be the most important effect of acute 1,2-dichloroethene exposure (ACGIH, 1980).

5.7. SUMMARY

There is limited evidence for the carcinogenicity of 1,1-dichloroethene. Significantly increased incidences of kidney adenocarcinomas, a rare tumor type, occurred in male Swiss mice exposed to 25 ppm 1,1-dichloroethene 4 hours/day, 5 days/week for 52 weeks followed by lifetime observation (Maltoni et al., 1985). Carcinogenicity of 1,1-dichloroethene was not demonstrated in numerous other studies with mice (strains other than Swiss), rats or hamsters, including NTP (1982) gavage bioassays with mice and rats. Activity as a tumor initiator in mouse skin, however, has been reported (Van Duuren et al., 1979). A retrospective mortality study of a cohort of 138 1,1-dichloroethene workers did not find exposure-related carcinogenicity, but design limitations preclude definite conclusions of noncarcinogenicity. Information regarding the carcinogenicity of 1,2-dichloroethene could not be located in the available literature as cited in the Appendix.

Mutagenicity of 1,1-dichloroethene has been demonstrated in numerous assays with different strains of S. typhimurium (Bartsch et al., 1975, 1979; Oesch et al., 1983; McCarroll et al., 1983; Jones and Hathway, 1978b; Cerna and Kypenova, 1977; Baden et al., 1976, 1977, 1978; Simmon et al., 1977; Malaveille et al., 1977; Waskell, 1978). 1,1-Dichloroethene also produced reverse mutation in E. coli WP2uvrA (Jones and Hathway, 1978b), forward mutations in E. coli K12 (Greim et al., 1975) and mutations in the yeast S. cerevisiae D7 (Bronzetti et al., 1981). 1,1-Dichloroethene has been reported to induce SCEs in cultured Chinese hamster ovary cells (McCarroll et al., 1983), but did not produce mutations to 8-azaquanine or oubain resistance in cultured V79 Chinese hamster cells (Drevon and Kuroki, 1979), dominant lethal mutations in rats (Short et al., 1977a) or mice (Anderson et al., 1977) exposed by inhalation, or chromosomal aberrations in bone marrow

cells of mice exposed by inhalation (Cerna and Kypenova, 1977). Limited evidence suggests that cis-1,2-dichloroethene is mutagenic when tested with *in vivo* metabolic activation systems. Mutagenicity was reported in host-mediated assays with *S. typhimurium* (Cerna and Kypenova, 1977) and *S. cerevisiae* (Bronzetti et al., 1984), but activity was not demonstrated with the trans-isomer in the same studies. cis-1,2-Dichloroethene and trans-1,2-dichloroethene were not mutagenic in reverse mutation assays with *S. typhimurium* (Cerna and Kypenova, 1977), forward and reverse mutation assays with *E. coli* (Greim et al., 1975) or assays with *S. cerevisiae* (Galli et al., 1982; Bronzetti et al., 1984) when tested with or without added metabolic activation preparations. Repeated intraperitoneal injections of cis-1,2-dichloroethene to mice produced chromosomal aberrations in the bone marrow, but similar treatment with the trans-isomer was not clastogenic (Cerna and Kypenova, 1977).

Teratogenic effects were not observed in the offspring of rats exposed to 200 ppm (200 mg/ℓ) 1,1-dichloroethene in the drinking water, or in offspring of rats or rabbits exposed by inhalation to ≤160 ppm (630 mg/m³), 7 hours/day on days 6-15 of gestation (Murray et al., 1979). Embryo/fetotoxicity was evident among the rats that inhaled 80 or 160 ppm (320 or 630 mg/m³) (delayed ossification of skull and cervical vertebrae centra, wavy ribs) and rabbits that inhaled 160 ppm (increased resorptions), but these effects did not occur without maternal toxicity. Incomplete ossification of fetal sternebrae and maternal toxicity occurred in another inhalation study with rats exposed to 15-449 ppm (59-1780 mg/m³) and mice exposed to 15-300 ppm (59-1190 mg/m³) 1,1-dichloroethene for 23 hours/day on days 6-16 of gestation (Short et al., 1977b). A 3-generation reproduction study showed that drinking water containing 50-200 ppm (50-200 mg/ℓ) 1,1-dichloroethene

produced hepatotoxic effects in adult rats but no effect on reproduction or neonatal development (Nitschke et al., 1980). Information regarding teratogenicity or other reproductive effects of 1,2-dichloroethene could not be located in the available literature as cited in the Appendix.

Chronic oral or inhalation administration of 1,1-dichloroethene to rats and mice produced toxic effects primarily in the liver. Hepatic alterations that include congestion, hypertrophy, hemorrhages, fatty degeneration, atrophy and necrosis were described in mice exposed by gavage to 10 mg/kg/day, 5 days/week for 104 weeks (NTP, 1982), rats exposed continuously through drinking water to 50-200 ppm (50-200 mg/ℓ) for 2 years (Rampy et al., 1977; Humiston et al., 1978; Quast et al., 1983), rats exposed by gavage to 50 mg/kg, 1 day/week for 120 weeks (Ponomarkov and Tomatis, 1980), rats exposed by inhalation to ~25 or 75 ppm (~100 or 300 mg/m^3), 6 hours/day, 5 days/week for 18 months with 6 months observation (Rampy et al., 1977; McKenna et al., 1982; Quast et al., 1986), and rats and mice exposed by inhalation to 55 ppm (220 mg/m^3), 6 hours/day, 5 days/week for 12 months (Lee et al., 1977). Kidney alterations including chronic inflammation in rats exposed by gavage to 5 mg/kg/day, 5 days/week for 104 weeks (NTP, 1982) and congestion in rats exposed by gavage to 50 mg/kg once weekly for 120 weeks (Ponomarkov and Tomatis, 1980) have also been reported. Hong et al. (1981) observed increased mortality and early terminations that were due to moribundity in rats and mice during 12-month observation periods following inhalation exposure to 55 ppm (220 mg/m^3) 1,1-dichloroethene, 6 hours/day, 5 days/week for 10 months (rats) or 6 months (mice). Adenomatous hyperplasia of the respiratory epithelia was observed in hamsters exposed to 25 ppm (100 mg/m^3) 1,1-dichloroethene, 4 hours/day, 4-5 days/week for 52

weeks with 105 weeks observation (Maltoni et al., 1985). Continuous inhalation exposure to 47 ppm (190 mg/m³) 1,1-dichloroethene for 90 days produced depressed growth in rats, guinea pigs, rabbits, monkeys and dogs, increased liver alkaline phosphaste and SGPT activities in rats and guinea pigs, hepatic effects including fatty changes and necrosis in rats, monkeys and dogs, and hypertrophy of the renal tubule epithelium in rats (Prendergast et al., 1967). Nonacute toxicity data for 1,2-dichloroethene are limited to two conflicting subchronic inhalation toxicity studies. An unpublished report indicates that exposure to 500 or 1000 ppm (2000 or 4000 mg/m³) 1,2-dichloroethene (60% cis- and 40% trans-isomer mixture) for 6 months (7 hours/day, 5 days/week) did not produce adverse effects on numerous parameters in rats, rabbits, guinea pigs or dogs (Torkelson, 1965). Freundt et al. (1977) reported fatty changes in the liver and pulmonary damage in rats exposed to 200 ppm (800 mg/m³) trans-1,2-dichloroethene (8 hours/day, 5 days/week) for 16 weeks.

6. AQUATIC TOXICITY

6.1. ACUTE

The available data concerning acute toxicity of dichloroethene to aquatic animals are presented in Table 6-1. There are few data for 1,2-dichloroethene, but the 96-hour LC_{50} values from the two studies (U.S. EPA, 1978) where both the 1,1- and 1,2-isomers were tested indicate that the 1,1-isomer is about twice as toxic as the 1,2-isomer to the bluegill, Lepomis macrochirus, and the waterflea, Daphnia magna. The lowest reported acutely toxic concentration was 2.4 mg/ℓ of 1,1-dichloroethene, at which some toxic effects were observed in Daphnia magna (LeBlanc, 1980; U.S. EPA, 1978). Three saltwater species were tested with the 1,1-isomer, and all showed similar sensitivity. The 96-hour LC_{50} values were 224-250 mg/ℓ (see Table 6-1).

6.2. CHRONIC

The only data concerning chronic toxicity of dichloroethenes were provided by a fathead minnow, Pimephales promelas, embryo-larval bioassay with 1,1-dichloroethene (U.S. EPA, 1978, 1980c). In this study, no adverse effects occurred at the highest concentration tested, 2.8 mg/ℓ.

6.3. PLANTS

U.S. EPA (1978) reported that the 96-hour EC_{50} for effects on cell numbers or chlorophyll was >798 mg/ℓ of 1,1-dichloroethene for the freshwater alga, Selenastrum capricornutum; however, the NOEC for this species was <80 mg/ℓ. For the saltwater alga, Skeletonema costatum, the 96-hour EC_{50} was >712 mg/ℓ, which was a NOEC.

TABLE 6-1

Acute Toxicity of Dichloroethenes to Aquatic Organisms

Species	Isomer	Toxic Concentration (mg/ℓ)	NOEC (mg/ℓ)	Effect	Reference
FRESHWATER SPECIES					
Bluegill	1,1	220	NR	96-hour LC_{50}	Dawson et al., 1977
Lepomis macrochirus	1,1	73.9	32		Buccafusco, 1981;
	1,2	135	<100		U.S. EPA, 1978
Fathead minnow	1,1	169	NR	96-hour LC_{50}, static	Dill et al., 1980
Pimephales promelas	1,1	108	NR	96-hour LC_{50}, flowthrough	
	1,1	29	NR	lethal threshold (7- to 13-day LC_{50})	
Waterflea	1,1	11.6	NR	48-hour LC_{50}	Dill et al., 1980
Daphnia magna	1,1	79	<2.4		LeBlanc, 1980;
	1,2	218	<110		U.S. EPA, 1978
SALTWATER SPECIES					
Sheepshead minnow *Cyprinodon variegatus*	1,1	249	79.8	96-hour LC_{50}	Heitmuller et al., 1981; U.S. EPA, 1978
Tidewater silverside *Menidia beryllina*	1,1	250	NR	96-hour LC_{50}	Dawson et al., 1977
Mysid shrimp *Mysidopsis bahia*	1,1	224	14.2	96-hour LC_{50}	U.S. EPA, 1978

NR = Not reported

6.4. RESIDUES

The only data concerning dichloroethene residues in aquatic biota were provided by Ferrario et al. (1985), who reported that the clam, Ranga cuneata, in Lake Ponchartrain, LA, contained an average of 4.4 ppb 1,1-dichloroethene.

6.5. SUMMARY

The information concerning the aquatic toxicity of dichloroethenes is limited. Results of studies with bluegills and Daphnia magna suggest that 1,1-dichloroethene is about twice as acutely toxic as 1,2-dichloroethene (U.S. EPA, 1978). Daphnia magna was the most sensitive species tested, having a NOEC of <2.4 mg/ℓ (LeBlanc, 1980; U.S. EPA, 1978). The only chronic toxicity data available indicated that fathead minnows were unaffected by concentrations of ≤2.8 mg/ℓ in an embryo-larval test. Two algal species tested were less susceptible to the effects of 1,1-dichloroethene exposure than any of the animal species (U.S. EPA, 1978).

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

The ACGIH (1982, 1985) recommends a TLV (8-hour TWA) of 5 ppm and a STEL of 20 ppm for 1,1-dichloroethene. NIOSH and OSHA jointly recommend limiting occupational exposure to the lowest possible level (NIOSH, 1978), but OSHA has not promulgated an exposure limit.

A carcinogenic potency factor (q_1^*) of 1.16 $(mg/kg/day)^{-1}$ for 1,1-dichloroethene was recently determined by CAG using the Maltoni et al. (1985) incidence data for kidney adenocarcinomas in mice (U.S. EPA, 1985). Earlier U.S. EPA assessments (U.S. EPA, 1980c, 1983a,b) used interim results of the same study to derive q_1^*s for 1,1-dichloroethene. Based on a q_1^* of 1.04 $(mg/kg/day)^{-1}$ for 1,1-dichloroethene, the U.S. EPA (1980c) calculated concentrations in water of 0.33, 0.033 and 0.003 µg/ℓ associated with excess cancer risks of 10^{-5}, 10^{-6} and 10^{-7}, respectively. An ADI of 0.2 mg/day was calculated for 1,1-dichloroethene using a NOAEL from the Prendergast et al. (1967) subchronic inhalation study (U.S. EPA, 1983b) because the evidence for carcinogenicity was considered questionable; this was done before the CAG (U.S. EPA, 1985) assessment. A chronic toxicity RQ of 1000 was calculated for 1,1-dichloroethene in 1983 (U.S. EPA, 1983c).

The ACGIH (1980, 1985) recommends a TLV (8-hour TWA) of 200 ppm and a STEL of 250 ppm for 1,2-dichloroethene. NIOSH occupational exposure criteria were not available, but OSHA limits exposure to an 8-hour TWA of 200 ppm (CFR, 1985). The U.S. EPA (1980c) did not promulgate an ambient water quality criterion for the isomers of 1,2-dichloroethene. A chronic toxicity RQ of 1000 was calculated for 1,2-dichloroethene on the basis of the Freundt et al. (1977) subchronic inhalation LOAEL for trans-1,2-dichloroethene in rats (U.S. EPA, 1983c).

7.2. AQUATIC

The U.S. EPA (1980c) did not derive an ambient water quality criterion for dichloroethenes for the protection of aquatic life.

8. RISK ASSESSMENT

8.1. 1,1-DICHLOROETHENE

Evidence for the carcinogenicity of 1,1-dichloroethene was found in an inhalation study with mice (Maltoni et al., 1985). In this study, male and female Swiss mice were exposed to 0, 10 or 25 ppm 1,1-dichloroethene for 4 hours/day, 4-5 days/week for 52 weeks followed by lifetime observation. As detailed in Table 5-1, a statistically significant increase in kidney adenocarcinomas occurred in the high-dose males. The incidences of mammary carcinomas in the females at both dose levels and pulmonary adenomas in both sexes at both dose levels were also significantly increased, but the responses were not clearly related to dose. Statistically significant increases in mammary tumors were also found in two inhalation and one gavage study with Sprague-Dawley rats (Maltoni et al., 1985; Rampy et al., 1978; Quast et al., 1983) (see Table 5-2) but these increases were not considered to be treatment-related because the background incidences of mammary tumors were high. Van Duuren et al. (1979) found that a single 121 mg application of 1,1-dichloroethene to the skin of mice followed by repeated applications of the tumor-promoting agent phorbol myristate acetate produced local papillomas.

Ten inhalation and seven oral (one drinking water, six gavage) studies did not demonstrate statistically significant increases of tumors (with the exception of the equivocal increases in mammary tumors cited above) (see Table 5-2). The inhalation studies, however, had deficiencies that included shortened exposure or observation periods, less than MTDs and single dose levels (U.S. EPA, 1985). Only two of the oral studies were multiple dose lifetime studies and the dosing appears to be less than the MTD. Thrice weekly skin applications did not produce significant increases in [illegible]

A limited retrospective mortality study of a population of 138 workers exposed primarily to 1,1-dichloroethene reported no carcinogenic effects (Ott et al., 1976). Deficiencies that included small cohort size and limited latency period, however, do not allow definitive conclusions to be drawn from this study.

Although the evidence for carcinogenicity is limited (IARC Group 3, CAG Group C chemical) (Section 9.2.1.), positive mutagenicity data (see Section 5.2.1.), activity as a tumor initiator in mouse skin (Van Duuren et al., 1979) and the ability of its metabolites to react with DNA (see Section 4.3.1.) support a potential genotoxic mechanism of action for 1,1-dichloroethene. The negative results from the large number of carcinogenicity/chronic toxicity studies are not inconsistent with potential genotoxicity since all of the negative studies are, as indicated, flawed in their sensitivity to detect a carcinogenic response (U.S. EPA, 1985).

U.S. EPA (1985) used the Maltoni et al. (1985) Swiss mice inhalation study as the basis of a quantitative cancer risk estimate for 1,1-dichloroethene under the presumption that the chemical is carcinogenic to humans. Using the incidence data for kidney adenocarcinomas in male mice and the multistage model developed by Kenneth Crump and adopted by the U.S. EPA (Howe and Crump, 1982), a q_1^* of 1.16 $(mg/kg/day)^{-1}$ was calculated. The corresponding estimate for a lifetime continuous exposure to 1 $\mu g/m^3$ of 1,1-dichloroethene was calculated to be 5.0×10^{-5} $(\mu g/m^3)^{-1}$. Potency factors (q_1^*) for water ingestion were also calculated from the negative carcinogenicity data in the Quast et al. (1983) lifetime drinking water study with Sprague-Dawley rats (total tumors in males) and the lifetime gavage study with F344 rats (adrenal pheochromocytomas and subcutaneous fibromas in males and mice lymphomas in females [see Table 6-21]). The

highest q_1^* was 0.577 $(mg/kg/day)^{-1}$, calculated from the incidences of adrenal pheochromocytomas in the male rats in the NTP (1982) bioassay. The corresponding unit risk for lifetime continuous exposure to 1 µg/ℓ was calculated as 1.66×10^{-5}. Although based on tumor incidences that were not statistically significant (NTP, 1982) or based on the incidence of total tumors in the Quast et al. (1983) study, an approach not ordinarily considered appropriate for derivation of potency factors, the U.S. EPA (1985) considered the oral route of administration in these studies more appropriate for extrapolating to drinking water exposure than the Maltoni et al. (1985) inhalation data. Using the q_1^* of 0.577 $(mg/kg/day)^{-1}$, concentrations in drinking water of 6.07×10^{-4}, 6.07×10^{-5} and 6.07×10^{-6} mg/ℓ are associated with excess cancer risks of 10^{-5}, 10^{-6} and 10^{-7}, respectively.

8.2. 1,2-DICHLOROETHENE

Information regarding the carcinogenicity or chronic toxicity of cis- or trans-1,2-dichloroethene were not available. Subchronic inhalation toxicity studies of trans-1,2-dichloroethene (Freundt et al., 1977) and what appears to be a mixture of 60% cis- and 40% trans-isomers (Torkelson, 1965), have been conducted, but inconsistencies in the results of these studies preclude derivation of an ADI. In the Freundt et al. (1977) study, 5/6 female Wistar rats exposed to 200 ppm (800 mg/m³) trans-1,2-dichloroethene, 8 hours/day, 5 days/week for 16 weeks had fatty changes in the liver (accumulation in the lobules and Kupffer cells). Lung damage (capillary hyperemia, alveolar septum distention, severe pneumonic infiltration) occurred in all six of the treated rats. Similar liver and lung alterations occurred in 2/6 and 0/6 control rats exposed to 0 ppm. In the unpublished study reported by

mg/m³) 1,2-dichloroethene vapor (60%-cis, 40% trans-isomers), 7 hours/day, 5 days/week for 6 months did not produce adverse effects (various endpoints including clinical chemistry and gross and histopathological examinations were assessed) in rats, rabbits, guinea pigs or dogs. The high-dose (1000 ppm) group is therefore exposed to a minimum of 400 ppm (1600 mg/m³) of trans-1,2-dichloroethene, a no affect level that is higher than the 200 ppm adverse effect level in the Freundt et al. (1977) study. Because of conflicting effect levels and limitations of the studies [small number of animals and short exposure duration in the Freundt et al. (1977) study] and an inadequately reported unpublished study (Torkelson, 1965), it is inappropriate to derive an ADI for trans-1,2-dichloroethene. It is also inappropriate to derive an ADI for cis-1,2-dichloroethene using the Torkelson (1965) no-effect data for the cis/trans-isomer mixture because subchronic or chronic toxicity data, indicating differences in toxicity between the isomers are not available. Acute inhalation data conflict on whether there is a significant difference between the toxicity of the two isomers (Torkelson and Rowe, 1981). A TLV of 200 ppm for 1,2-dichloroethene (stereoisomer mixture) (ACGIH, 1980) is based on the Torkelson (1965) toxicity data. It is inappropriate to use the TLV to derive an ADI until further information becomes available to clarify or support the Torkelson (1965) data. The ADI is now most often referred to as the Reference dose (RfD).

9. REPORTABLE QUANTITIES

9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

9.1.1. 1,1-Dichloroethene. Chronic oral or inhalation administration of 1,1-dichloroethene to rats and mice produced toxic effects primarily in the liver (Table 9-1). Hepatic alterations that include congestion, hypertrophy, hemorrhages, fatty degeneration, atrophy and necrosis were described in mice exposed by gavage to 10 mg/kg/day, 5 days/week for 104 weeks (NTP, 1982), rats exposed continuously through drinking water to 50-200 ppm for 2 years (Rampy et al., 1977; Humiston et al., 1978; Quast et al., 1983), rats exposed by gavage to 50 mg/kg for 1 day/week for 120 weeks (Ponomarkov and Tomatis, 1980), rats exposed by inhalation to ~25 or 75 ppm (100 or 300 mg/m^3) for 6 hours/day, 5 days/week for 18 months with 6 months observation (Rampy et al., 1977; McKenna et al., 1982; Quast et al., 1986), and rats and mice exposed by inhalation to 55 ppm (220 mg/m^3), 6 hours/day, 5 days/week for 12 months (Lee et al., 1977). Kidney alterations include chronic inflammation in rats exposed by gavage to 5 mg/kg/day, 5 days/week for 104 weeks (NTP, 1982) and congestion in rats exposed by gavage to 50 mg/kg once weekly for 120 weeks (Ponomarkov and Tomatis, 1980). Hong et al. (1981) observed increased mortality and early terminations that were due to moribundity in rats and mice during 12-month observation periods following inhalation exposure to 55 ppm (220 mg/m^3) 1,1-dichloroethene 6 hours/day, 5 days/week for 10 months (rats) or 6 months (mice). The numbers of deaths and early terminations in the treated male and female rats were 11/14 (79%) and 9/16 (56%), respectively, vs. 6/16 (38%) and 7/16 (44%) in respective controls. Mortality/early terminations in the treated male and female mice were 6/12 (50%) and 5/12 (42%), respectively, vs. 6/28 (21%) and 5/28 (18%) in respective controls. Causes were not indicated but tumor incidences were

TABLE 9-1

Chronic Toxicity Summary for 1,1-Dichloroethene

Ro	ecies/ train	Number/Sex	Vehicle	Purity	Treatment	Dose[a] (mg/kg/day)	Response	Reference
Oral (gav	t/ 44/N	50/M or F	corn oil	99%	0, 1 or 5 mg/kg/day, 5 days/week for 104 weeks	0, 0.7 or 3.6	Chronic renal inflammation in high-dose males and females	NTP, 1982
Oral	t/ rague- wley	48/M or F (80/sex in controls)	drinking water	≥99.5%	0, 50, 100 or 200 ppm (nominal) for 2 years	0, 7, 10 or 20 (M)[b]; 0, 9, 14 or 30 (F)[b]	Hepatocellular fatty changes and periportal hepatocellular hypertrophy at all doses in females and in high-dose males; centrilobular atrophy in livers in high-dose females	Rampy et al., 1977; Humiston et al., 1978; Quast et al., 1983
Oral (gav	t/ rague- wley	50/M or F (100/sex in controls)	olive oil	99.95%	0, 5, 10 or 20 mg/kg/day, 4-5 days/ week for 52 weeks; 95 weeks observation	0, 3.2, 6.4 or 12.9	No treatment-related effects	Maltoni et al., 1985
Oral (gav	t/ rague- wley	50/M or F (82 M, 77 F in controls)	olive oil	99.95%	0 or 0.5 mg/kg/day, 4-5 days/ week for 52 weeks; 95 weeks observation	0 or 0.3	No treatment-related effects	Maltoni et al., 1985
Oral (gav	t/BDIV	64-90/M or F	olive oil	99%	0 or 150 mg/kg on maternal day 17 of gestation; from weaning, 0 or 50 mg/ kg, 1 day/week for 120 weeks	0 or 7.1	Liver hemorrhages, multiple lobular necroses and parenchymal cell degeneration; lung and kidney congestion	Ponomarkov and Tomatis, 1980
Oral (gav	use/ C3H	50/M or F	corn oil	99%	0, 2 or 10 mg/kg/day, 5 days/week for 104 weeks	0, 1.4 or 7.1	Liver necrosis (focal, multi- focal or diffuse) in high-dose males	NTP, 1982
Inha	t/ rague- wley	85-86/ M or F	NA	≥99%	0, 25 or 75 ppm[c] (0, 100 or 300 mg/m³), 6 hours/day, 5 days/ week for 18 months; 6 months observation	0, 5.7 or 17.1	Decreased liver weight in males at both doses at 12-month sacri- fice; hepatocellular fatty changes in both sexes at both doses at 6-, 12- or 18-month sacrifices, but not after 6 months without treatment	Rampy et al., 1977; McKenna et al., 1982; Quast et al., 1986
Inha	t/CD	36/M or F	NA	99.8%	0 or 55 ppm (0 or 220 mg/m³), 6 hours/ day, 5 days/week for 12 months	0 or 8.8	Hepatocellular fatty changes	Lee et al., 1977

TABLE 9-1 (cont.)

Rout	les/ ain	Number/Sex	Vehicle	Purity	Treatment	Dose[a] (mg/kg/day)	Response	Reference
Inhal	/CD	36/M or F	NA	99.8%	0 or 55 ppm (0 or 220 mg/m³), 6 hours/day, 5 days/week for 10 months; 12 months observation	0 or 12.5	Increased deaths and early terminations when moribund during observation period; cause not reported	Hong et al., 1981
Inhal	gue- ley	36/M or F (100/sex in controls)	NA	99.95%	0, 10, 25, 50 or 100 ppm (0, 40, 100, 200 or 400 mg/m³), 4 hours/day, 4-5 days/ week for 52 weeks; 85 weeks observation	0, 1.4, 3.4, 6.8 or 13.7	Treatment-related nonneoplastic effects not indicated	Maltoni et al., 1985
Inhal	se/	36/M or F	NA	99.8%	0 or 55 ppm (0 or 220 mg/m³), 6 hours/ day, 5 days/week for 12 months	0 or 19.1	Enlarged basophilic hepatocytes, enlarged abnormal nuclei, focal degeneration and necrosis in liver	Lee et al., 1977
Inhal	se/	8 or 12/ M or F	NA	99.8%	0 or 55 ppm (0 or 220 mg/m³), 6 hours/ day, 5 days/week for 6 months; 12 months observation	0 or 25.5	Increased deaths and early termination when moribund during observation period; cause not reported	Hong et al., 1981
Inhal	se/ ss	30-120[d]/ M or F	NA	99.95%	0, 10 or 25 ppm (0, 40 or 100 mg/m³), 4 hours/day, 4-5 days/week for 52 weeks; 69 weeks observation	0, 2.8 or 7.0	Treatment-related nonneoplastic effects not indicated	Maltoni et al., 1985
Inhal	ster/ nese	17-30/ M or F	NA	99.95%	0 or 25 ppm (0 or 100 mg/m³), 4 hours/ day, 4-5 days/week for 52 weeks; 105 weeks observation	0 or 5.8	Adenomatous hyperplasia of respiratory epithelia (primarily in males)	Maltoni et al., 1985

[a]Dose ation studies calculated using inhalation rates of 0.223 m³/day for rats, 0.039 m³/day for mice and an assumed absorption coefficient of 1 rats d body weights (0.35 kg for rats, 0.03 kg for mice, 0.12 kg for hamsters) were used except in the Lee et al. (1977) studies (0.5 kg for r mice)

[b]Repo ntake

[c]Rats nd 75 ppm groups were exposed to 10 and 40 ppm, respectively, for the first 42 days of exposure

[d]Grou 30 and 30 sixteen-week-old mice of each sex exposed to 0, 10 and 25 ppm, respectively. Groups of 90 and 120 nine-week-old mice of each sex and 25 ppm, respectively

NA = le

not significantly increased and hepatic effects occurred in a related study without an observation period (Lee et al., 1977). Adenomatous hyperplasia of the respiratory epithelia was observed in hamsters exposed to 25 ppm (100 mg/m³) 1,1-dichloroethene, 4 hours/day, 4-5 days/week for 52 weeks with 105 weeks observation (Maltoni et al., 1985).

Prendergast et al. (1967) exposed several species of animals to 90-day continuous exposures of 0, 20, 61, 101 or 189 mg/m³. Treatment groups included 15 Long-Evans or Sprague-Dawley rats, 15 Hartley guinea pigs, 3 or 9 squirrel monkeys, 2 beagle dogs and 3 New Zealand rabbits (189 mg/m³ only). Controls consisted of 304 rats, 314 guinea pigs, 57 monkeys, 34 dogs and 48 rabbits. Treatment-related effects occurred at the high dose and included depression of growth in all species, elevated liver alkaline phosphatase and SGPT activities in rats and guinea pigs, hepatic alterations (fatty metamorphoses, focal necrosis, hemosiderin deposition, lymphocytic infiltration, bile duct proliferation, fibrosis and pseudo-lobule formation) in rats, monkeys and dogs, and renal alterations (nuclear hypertrophy of the tubule epithelium) in rats.

Fetotoxicity/teratogenicity studies of 1,1-dichloroethene have also been conducted. Murray et al. (1979) exposed 24-26 Sprague-Dawley rats to 0 or 200 ppm (0 or 200 mg/ℓ) 1,1-dichloroethene in the drinking water on days 6-15 of gestation and examined fetuses on day 21. The treated dams reportedly consumed ~40 mg/kg/day 1,1-dichloroethene. Fetal lengths were significantly increased in the exposed group. Maternal toxicity (altered body and liver weights) or treatment-related effects on numbers of litters, implantation sites/dam, live fetuses/litter, resorptions/litter, corpora lutea/dam, fetal sex ratio, fetal body weights or fetal development were not evident.

Sprague-Dawley rats and New Zealand rabbits were exposed to 0, 20, 80 or 160 ppm (0, 80, 320 or 630 mg/m³) 1,1-dichloroethene by inhalation for 7 hours/day on days 6-15 of gestation (Murray et al. 1979). The maternal and fetal rats and rabbits were evaluated as in the drinking water study. In the rat study, the treatment group sizes were 44 (20 ppm) or 30 (80 and 160 ppm), and 20-47 untreated rats/dose served as controls. Increased incidences of fetal skeletal alterations (delayed ossification of skull and cervical vertebral centra, wavy ribs) occurred at 80 and 160 ppm with signs of maternal toxicity (decreased food consumption and weight gain at 80 and 160 ppm, increased liver weight at 160 ppm). Groups of 16-22 animals were used in the rabbit study. Maternal toxicity was indicated by decreased body weights at 80 and 160 ppm and increased liver weights at 80 ppm, but fetotoxic or developmental effects were not observed. The number of resorptions/litter was significantly increased at 160 ppm, but this may have been due to maternal toxicity rather than fetal exposure.

Short et al. (1977b) exposed CD rats and CD-1 mice by inhalation to 0, 15, 57, 300 or 449 ppm (0, 59, 230, 1200 or 1780 mg/m³) 1,1-dichloroethene and 0, 15, 30, 57, 144 or 300 ppm (0, 59, 120, 230, 571 or 1200 mg/m³) 1,1-dichloroethene, respectively, for 23 hours/day on days 6-16 of gestation. There were ~20 animals in the exposed groups and 60 in the control groups. The rats and mice were sacrificed on gestation days 20 and 17, respectively. In rats, an appreciable number of maternal deaths (25%) occurred at 300 and 449 ppm and food consumption and weight gain was decreased at $\geq$15 ppm. Similar effects occurred in mice with 100% maternal mortality at 144 or 300 ppm and reduced food consumption and weight gain in all groups except 15 ppm. Early resorptions were common in all exposed groups with 100% resorption in mice exposed to 30 and 57 ppm and 49 and 64%

abnormalities were not seen in surviving pups of either species. Some soft-tissue anomalies were observed in rats at 15 and 57 ppm, but incidences were not statistically significant. Significantly increased incidences of incomplete ossification of sternebrae occurred in mice at the 15 ppm level and in rats at the 15, 57 and 300 ppm levels. Since interpretation of these effects was complicated by the maternal toxicity, another study was conducted with shorter exposures in mice (Short et al., 1977b). 1,1-Dichloroethene was administered on gestation days 6-15 (54 ppm; 210 mg/m^3), 8-15 (41, 54 and 74 ppm; 160, 210 and 290 mg/m^3), 10-15 (54 ppm; 210 mg/m^3), 12-15 (54 ppm), 6-9 (56, 81 and 112 ppm; 220, 320 and 444 mg/m^3), 9-12 (56, 81 and 112 ppm), 12-15 (56, 81 and 112 ppm) and 15-17 (56, 81 and 112 ppm). Incidences of resorption were decreased by the shortened exposure periods but the weight loss in treated dams was still evident. Significantly increased incidences of cleft palate occurred at the 54 ppm level from gestation days 10-15 and 12-15. Other abnormalities included ossification problems as described above and immature skin and hematomas. Interpretation of these results is complicated because some of these anomalies were also observed in some groups of animals that served as diet-restricted controls and because of the occurrence of maternal toxicity at nearly all concentrations of 1,1-dichloroethene used.

The above studies indicate that liver and kidney histological alterations, fetotoxicity and mortality in rats and mice can be used to calculate CSs and RQs for 1,1-dichloroethene (Table 9-2). Animal oral dosages in mg/kg/day were adjusted for partial weekly exposures and converted to human MEDs by multiplying by the cube root of the ratio of animal body weight to reference human body weight (70 kg), and by 70 kg to convert to units of mg/day. Default values of 0.35 and 0.03 kg were chosen as the reference

TABLE 9-2

Composite Scores for 1,1-Dichloroethene

Species/ Strain	Treatment	Human MED (mg/day)	RV_d	Effect	RV_e	CS	RQ	Reference
rat/ Sprague-Dawley	50 ppm (50 mg/ℓ) for 2 years	108	2.4	Hepatocellular fatty changes in females	5	12.0	1000	Rampy et al., 1977; Humiston et al., 1978; Quast et al., 1983
[illegible]	50 mg/kg/day, 1 day/ week for 120 weeks	85	2.6	Liver congestion, parenchymal cell degeneration, hyperplasia, necrosis; kidney congestion	6	15.6	1000	Ponomarkov and Tomatis, 1980
rat/ [illegible]	5 mg/kg/day, 5 days/ week for 104 weeks	43	3.0	Chronic renal inflammation	6	18.0	1000	NTP, 1982
mouse/ [illegible]	10 mg/kg/day, 5 days/ week for 104 weeks	43	3	Liver necrosis	6	18.0	1000	NTP, 1982
rat/ Sprague-Dawley	25 ppm (100 mg/m³), 6 hours/day, 5 days/ /week for 18 months with 6 months observation	136	2.3	Reversible hepatocellular fatty changes (not evident at end of observation period)	5	11.4	1000	Rampy et al., 1977; McKenna et al., 1982; Quast et al., 1986
rat/CD	55 ppm (220 mg/m³), 6 hours/day, 5 days/ week for 12 months	236	[illegible]	Hepatocellular fatty changes	5	9.5	1000	Lee et al., 1977
rat/CD	55 ppm (220 mg/m³), 6 hours/day, 5 days/ week for 10 months with 12 months observation	300	1.8	Early deaths and terminations when moribund during observation period; causes not reported	10	18.0	1000	Hong et al., 1981
rat/ Sprague-Dawley	80 ppm (320 mg/m³), 7 hours/day on days 6-15 of gestation	891	1.1	Fetal skeletal alterations (delayed ossification of skull and cervical vertebrae centra, wavy ribs) with maternal toxicity	8	8.8	1000	Murray et al., 1979
mouse/ [illegible]	55 ppm (220 mg/m³), 6 hours/day, 5 days/ week for 12 months	222	2.0	Enlarged basophilic hepatocytes and nuclei, focal degeneration and necrosis in liver	6	12.0	1000	Lee et al., 1977

TABLE 9-2 (cont.)

Species/ Strain	Treatment	Human MED (mg/day)	RV_d	Effect	RV_e	CS	RQ	Reference
[illegible]	55 ppm (220 mg/m³), 6 hours/day, 5 days/ week for 6 months with 12 months observation	259	1.9	Early deaths and terminations when moribund during observation period; causes not reported	10	19.0	1000	Hong et al., 1981
[illegible]	15 ppm (60 mg/m³), 23 hours/day, on days 6-16 of gestation	395	1.6	Incomplete ossification of sternebrae in fetuses with maternal toxicity	8	12.8	1000	Short et al., 1977

[illegible] measured water intake of 9 mg/kg/day for females

[illegible] measured body weights [0.35 kg for rats (average of both sexes), 0.045 kg for male mice]

[illegible] measured body weights [0.5 kg for rats (average of both sexes), 0.04 kg for mice (average of both sexes)]

[illegible] measured body weight (0.25 kg)

[illegible] reproduction study

body weights of rats and mice, respectively. Daily dosages (mg/kg/day) were calculated from the inhalation exposures by correcting for partial daily and weekly exposures, multiplying by assumed animal inhalation rates (0.223 m^3/day for rats, 0.039 m^3/day for mice) and dividing by animal body weight. Human MEDs were calculated as described above. CSs were calculated by multiplying the RV_d and RV_e associated with each MED as detailed in Table 9-2.

As detailed in Table 9-2, the effects documented in these studies result in CSs that range from 9.5-19, which correspond to an RQ of 1000. These effects include fatty alterations and necrosis in the liver (RV_es of 5 and 6, respectively) of rats and mice exposed orally and by inhalation, chronic inflammation in the kidney (RV_e of 6) in rats exposed orally, and abnormal ossification in fetuses with maternal toxicity (RV_e of 8) in rats and mice exposed by inhalation. Hepatotoxicity is a particularly well documented effect of 1,1-dichloroethene; however, only two of the inhalation studies (Rampy et al., 1977; McKenna et al., 1982) had treatment durations longer than 12 months, and the subchronic toxicity study of Prendergast et al. (1967) was not used to calculate RQs since adequate chronic data was not available.

The postexposure mortality (increased numbers of deaths and terminations from moribundity) in CD rats and CD-1 mice exposed by inhalation, 6 hours/day, 5 days/week to 55 ppm 1,1-dichloroethene for 10 or 6 months, respectively (Hong et al., 1981) yield CSs of 18 (rats) and 19 (mice). These studies were considered to be chronic for the MED calculations because the observation periods were 12 months and because pharmacokinetic data indicate that elimination of inhaled 1,1-dichloroethene (as metabolites or unmetabolized compound) by rats and mice is rapid and essentially complete (McKenna

et al., 1977). Use of this study as the basis of an RQ for 1,1-dichloroethene is not precluded by the lack of corroborating data in other studies (see Table 9-1) because different strains of animals were used or post-exposure observation was not conducted. Therefore, the highest CS, 23, which is calculated from the Hong et al. (1981) mouse study, should be used for the ranking of 1,1-dichloroethene (Table 9-3); however, this study did not give the highest CS in an earlier RQ document for 1,1-dichloroethene (U.S. EPA, 1983a). This is attributable to a different methodology for calculating human doses in mg/kg/day from inhalation exposure that assumed equivalent absorbed doses among species.

9.1.2. 1,2-Dichloroethene. Unpublished data (Torkelson, 1965) reported by ACGIH (1980) indicate that 500 or 1000 ppm (2000 or 4000 mg/m^3) of a mixture consisting of 60% cis- and 40% trans-1,2-dichloroethene did not produce adverse effects on growth, mortality, organ or body weights, hematology, clinical chemistry or gross or microscopic pathology in rats, rabbits, guinea pigs or dogs when inhaled for 7 hours/day, 5 days/week for 6 months. Additional information regarding this study was not reported. Freundt et al. (1977), however, described histological alterations in the liver and lungs of SPF Wistar rats that were exposed to 200 ppm (800 mg/m^3) of trans-1,2-dichloroethene for 8 hours/day, 5 days/week for 16 weeks. Of six exposed rats, three were reported to have severe accumulation of fat in the liver lobules and Kupffer cells and two rats had slight accumulation; slight fat accumulation was also reported in 2/6 control animals. Slight hyperemia and distention of the lung alveolar septum occurred in all of the treated rats but not in any of the controls. Additional information regarding the subchronic or chronic toxicity of 1,2-dichloroethene could not be located in the available literature as cited in the Appendix.

TABLE 9-3

1,1-DICHLOROETHENE

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	Inhalation
Dose*:	259 mg/day
Effect:	postexposure mortality and moribundity
Reference:	Hong et al., 1981
RV_d:	1.9
RV_e:	10
Composite Score:	19
RQ:	1000

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*Equivalent human dose

The reason for the discrepancy between the subchronic toxicity studies of Torkelson (1965) in which a NOAEL of 1000 ppm for a 60% cis- 40% trans-1,2-dichloroethene mixture was reported and Freundt et al. (1977) who reported an adverse effect level of 200 ppm trans-1,2-dichloroethene is unclear and cannot be resolved because of the inadequate description of the Torkelson (1965) study and the small group sizes and short duration of the Freundt et al. (1977) study. Acute inhalation data suggest that the trans-isomer is twice as toxic as the cis-isomer in rats (Smyth, 1956), but this in itself cannot account for the difference between the two subchronic studies.

Although not recommended because of the small group sizes and short duration, the LOAEL from the Freundt et al. (1977) study can be used to derive an RQ for 1,2-dichloroethene.

A MED of 12 mg/kg/day is calculated from the 200 ppm (800 mg/m^3) exposure by adjusting for partial daily (8 hours/day) and weekly (5 days/week) exposures, multiplying by assumed daily rat inhalation volume (0.223 m^3/day) and an assumed respiratory absorption coefficient of 0.5, dividing by assumed rat body weight (0.35 kg) and, additionally, dividing by an uncertainty factor of 10 since the duration was subchronic. Multiplying the animal MED by the cube root of the ratio of animal to human animal body weights and 70 kg yields a human MED of 144 mg/day. The RV_d corresponding to this MED is 2.3. An appropriate RV_e for the fat accumulation in the liver and histological lung alterations is 5. The CS, calculated as the product of the RV_d and RV_e, is 13.8, which corresponds to an RQ classification of 1000 (Table 9-4). The CS calculated in an earlier RQ document for 1,2-dichloroethene (U.S. EPA, 1983b) from the same study was lower

TABLE 9-4

1,2-DICHLOROETHENE

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	Inhalation
Dose*:	144 mg/day
Effect:	fat accumulation in the liver and histological alterations in the lungs
Reference:	Freundt et al., 1977
RV_d:	2.3
RV_e:	5
Composite Score:	13.8
RQ:	1000

*Equivalent human dose

(10.5); this is attributable to a different methodology for calculating human doses in mg/kg/day from inhalation exposure that assumed equivalent absorbed doses among species.

9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY

9.2.1. 1,1-Dichloroethene. Direct evidence for the carcinogenicity of 1,1-dichloroethene was found in an inhalation study with mice (Maltoni et al., 1985). In this study, male and female Swiss mice were exposed to 0, 10 or 25 ppm (0, 40 or 100 mg/m^3) 1,1-dichloroethene 4 hours/day, 4-5 days/week for 52 weeks followed by lifetime observation. As detailed in Table 5-1, a statistically significant increase in kidney adenocarcinomas occurred in the high-dose males. The incidences of mammary carcinomas in the females at both dose levels and pulmonary adenomas in both sexes at both dose levels were also significantly increased, but the responses were not clearly dose-related. Statistically significant increases in mammary tumors were also found in two inhalation and one gavage study with Sprague-Dawley rats (Maltoni et al., 1985; Rampy et al., 1978; Quast et al., 1983) (see Table 5-1) but these increases were not considered to be related to treatment because the background incidences of mammary tumors were high. Van Duuren et al. (1979) found that a single 121 mg application of 1,1-dichloroethene to the skin of mice followed by repeated applications of the tumor-promoting agent phorbol myristate acetate produced local papillomas.

Ten inhalation and seven oral (one drinking water, six gavage) studies did not demonstrate statistically significant increases in tumors (with the exception of the equivocal increases in mammary tumors cited above) (see Table 5-2). The inhalation studies, however, had deficiencies that included shortened exposure or observation periods, less than MTDs or single dose levels (U.S. EPA, 1985). Only two of the oral studies were multiple dose

lifetime studies and the dosing appears to be less than the MTD. Twice weekly skin applications did not produce significant increases in local or distant tumors (Van Duuren et al., 1979).

A limited retrospective mortality study of a population of 138 workers exposed primarily to 1,1-dichloroethene reported no carcinogenic effects (Ott et al., 1976). Deficiencies that include small cohort size and limited latency period, however, do not allow definitive conclusions to be drawn from this study.

Although the evidence for carcinogenicity is limited (IARC Group 3, CAG Group C chemical), positive mutagenicity data (U.S. EPA. 1985), its activity as a tumor initiator in mouse skin (Van Duuren et al., 1979) and the ability of its metabolites to react with DNA (U.S. EPA, 1985) support a potential genotoxic mechanism of action for 1,1-dichloroethene. The negative results from the large number of carcinogenicity/chronic toxicity studies are not inconsistent with potential genotoxicity since all of the negative studies are, as indicated above, flawed in their sensitivity to detect a carcinogenic response (U.S. EPA, 1985).

U.S. EPA (1985) used the Maltoni et al. (1985) Swiss mice inhalation study as the basis of a quantitative cancer risk assessment for 1,1-dichloroethene under the presumption that the chemical is carcinogenic to humans. Using the same dose-response data (kidney adenocarcinomas) as U.S. EPA (1985), an unadjusted $1/ED_{10}$ of 8.03 $(mg/kg/day)^{-1}$ was calculated using the multistage model developed by Kenneth Crump and adopted by the U.S. EPA (Howe and Crump, 1982) and the parameters summarized in Table 9-5. The F-factor, calculated by multiplying the unadjusted $1/ED_{10}$ by the cube root of the ratio of human body weight (assumed to be 70 kg) to assumed mouse body weight (0.035 kg), is calculated to be 101.2 $(mg/kg/day)^{-1}$.

TABLE 9-5

Derivation of Potency Factor (F)
Agent: 1,1-Dichloroethene

Reference:	Maltoni et al., 1985		
Exposure route:	inhalation		
Species:	mouse		
Strain:	Swiss		
Sex:	male		
Vehicle or physical state:	gas		
Body weight:	0.035 kg[a]		
Duration of treatment:	52 weeks		
Duration of study:	121 weeks		
Lifespan of animal:	121 weeks		
Target organ:	kidney		
Tumor type:	adenocarcinoma		
Experimental doses/exposure (ppm):	0	10	25
Transformed doses[b] (mg/kg/day):	0	0.078	0.195
Tumor incidence:	0/125[c]	0/25	28/119[c]
Unadjusted ED_{10}:	8.03 $(mg/kg/day)^{-1}$		
$1/ED_{10}$ (F factor):	101.2 $(mg/kg/day)^{-1}$		

[a]Estimated by U.S. EPA (1985)

[b]Transformation used mouse body burden data from McKenna et al. (1977) pharmacokinetic study as detailed in U.S. EPA (1985)

[c]Incidence from two control (0/56 and 0/70) and two treated (3/21 and 25/98) groups were combined since the incidences were not significantly different (U.S. EPA, 1985)

The limited evidence for carcinogenicity in animals and inadequate human evidence indicate that 1,1-dichloroethene should be classified in IARC Group 3 and CAG Group C (U.S. EPA, 1984). Because the F-factor is >100, 1,1-dichloroethene is placed in CERCLA Potency Group 1. Chemicals in Potency Group 1 and CAG Group C have a MEDIUM hazard ranking under CERCLA.

9.2.2. 1,2-Dichloroethene. Pertinent data regarding the carcinogenicity of 1,2-dichloroethene could not be located in the available literature as cited in the Appendix. Both isomers and an unspecified mixture have been scheduled for testing by the National Toxicology Program (NTP, 1985). 1,2-Dichloroethene has an IARC ranking of Group 3 meaning not classified and a CAG (U.S. EPA, 1984) ranking of Group D meaning not classified.

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Zhang, J., S. Hatakeyama and H. Akimoto. 1983. Rate constants of the reaction of ozone with trans-1,2-dichloroethene and vinyl chloride in air. Int. J. Chem. Kinet. 15(7): 655-668.

Zoeteman, B.C.J., E. DeGreef and F.J.J. Brinkman. 1981. Persistence of organic contaminants in ground water, lessons from soil pollution incidents in the Netherlands. Sci. Total Environ. 21: 187-202.

APPENDIX

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of the following:

CASR online (U.S. EPA Chemical Activities Status Report)
CAS online STN International
TOXLINE
TOXBACK 76
TOXBACK 65
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP
NTIS
Federal Register

These searches were conducted in October, 1985. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. Documentation of the Threshold Limit Values, 4th ed. (Includes Supplemental Documentation, 1981, 1982, 1983). Cincinnati, OH. 486 p.

ACGIH (American Conference of Governmental Industrial Hygienists). 1985. TLVs: Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1985-1986. Cincinnati, OH. 114 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2A. John Wiley and Sons, NY. 2878 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2B. John Wiley and Sons, NY. p. 2879-3816.

Clayton, G.D. and F.E. Clayton, Ed. 1982. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2C. John Wiley and Sons, NY. p. 3817-5112.

Grayson, M. and D. Eckroth, Ed. 1978-1983. Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed. John Wiley and Sons, NY. 23 Volumes.

Hamilton, A. and H.L. Hardy. 1974. Industrial Toxicology, 3rd ed. Publishing Sciences Group, Inc., Littleton, MA. 575 p.

IARC (International Agency for Research on Cancer). IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. WHO, IARC, Lyons, France.

ITII (International Technical Information Institute). 1982. Toxic and Hazardous Industrial Chemicals Safety Manual for Handling and Disposal with Toxicity and Hazard Data. ITII, Tokyo, Japan. 700 p.

NTP (National Toxicology Program). 1984. Toxicology Research and Testing Program. Chemicals on Standard Protocol. Management Status.

Ouellette, R.P. and J.A. King. 1977. Chemical Week Pesticide Register. McGraw-Hill Book Co., NY.

Sax, N.I. 1979. Dangerous Properties of Industrial Materials, 5th ed. Van Nostrand Reinhold Co., NY.

SRI (Stanford Research Institute). 1984. Directory of Chemical Producers. Menlo Park, CA.

U.S. EPA. 1985. Status Report on Rebuttable Presumption Against Registration (RPAR) or Special Review Process. Registration Standards and the Data Call in Programs. Office of Pesticide Programs, Washington, DC.

U.S. EPA. 1985. CSB Existing Chemical Assessment Tracking System. Name and CAS Number Ordered Indexes. Office of Toxic Substances, Washington, DC.

USITC (U.S. International Trade Commission). 1983. Synthetic Organic Chemicals. U.S. Production and Sales, 1982, USITC Publ. 1422, Washington, DC.

Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Co., NY.

Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

Windholz, M., Ed. 1983. The Merck Index, 10th ed. Merck and Co., Inc., Rahway, NJ.

In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

Battelle's Columbus Laboratories. 1971. Water Quality Criteria Data Book. Volume 3. Effects of Chemicals on Aquatic Life. Selected Data from the Literature through 1968. Prepared for the U.S. EPA under Contract No. 68-01-0007. Washington, DC.

Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. Summaries of Toxicity Tests Conducted at Columbia National Fisheries Research Laboratory. 1965-1978. U.S. Dept. Interior, Fish and Wildlife Serv. Res. Publ. 137, Washington, DC.

McKee, J.E. and H.W. Wolf. 1963. Water Quality Criteria, 2nd ed. Prepared for the Resources Agency of California, State Water Quality Control Board. Publ. No. 3-A.

Pimental, D. 1971. Ecological Effects of Pesticides on Non-Target Species. Prepared for the U.S. EPA, Washington, DC. PB-269605.

Schneider, B.A. 1979. Toxicology Handbook. Mammalian and Aquatic Data. Book 1: Toxicology Data. Office of Pesticide Programs, U.S. EPA, Washington, DC. EPA 540/9-79-003. NTIS PB 80-196876.